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U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
MARION B. FOLSOM, *Secretary*

PUBLIC HEALTH SERVICE
LEROY E. BURNEY, *Surgeon General*

Medical care expenditures of farm-operator families have increased sharply in the past 20 years, with a decrease in the farm-urban disparity, improvement in the relative position of southern families, and changes in the distribution of the medical care dollar.

Farm Medical Care Expenditures

JEAN L. PENNOCK, M.A.

FARM-OPERATOR families in 1955 spent, on the average, $240 per family for medical care. Spending per person in these families amounted to $63. Comparison of this figure with per person expenditures of $10 by farm families and $19 by urban families in 1935–36 (*1*), $15 by farm families and $32 by urban families in 1941 (*2*), and $65 by urban families in 1950 (*3*) reveals a tremendous increase in the level of expenditures in the past two decades and indicates that farm and urban families are becoming more similar in spending for medical care.

Part of this increase in medical care expenditures is due to the change in price level (*4*). But when this is taken into account, a tripling in medical expenditures for members of farm families since 1935–36 and a doubling since 1941 remain (table 1).

Beyond the rise in prices, it is difficult to pinpoint factors that explain the change in medical care expenditures. It is easier to point out some of the things that are not responsible.

Only part of the change can be attributed to an increase in the income of the farm population; although the real income of farmers rose rapidly during the early years of the war and remained relatively constant at a high level from 1943 through 1946, it then began a slow decline that, with interruptions, continued through 1955 and brought it in that year to a point only about 20 percent above the 1941 figures (*5*). Only fragmentary data are available on the movement of farm-family expenditures for medical care between 1941 and 1955, but indications are that in dollars of constant purchasing power they have risen more or less continuously throughout the period. An estimate for the farm population in 1945, derived from a survey in the North Central region and in the South, would indicate that at that time medical care expenditures were far short of the 1955 level. Home accounts of a group of farm families submitting their records to State universities show that the medical care expenditures of this group rose steadily throughout the period (*6*). These account-keeping families are not typical of all farm families, but it is assumed that their accounts reflect the trend in farm spending.

Our aging population might be expected to push medical costs upward, but on examination the effect of the change in the age distribution of the farm population is found to be negligible. Increases in the proportion of children, the age group with the lowest average expenditures, appear to cancel out increases at the other end of the age range, where expenditures tend to be high. This conclusion assumes the relationships in expenditures by age found by Mushkin in the 1950 urban data (*7*).

The explanation for the increase in farm expenditures for medical care must be sought

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in part in the wide complex of factors determining the general living expenses among farm families, for the medical care situation is not an isolated phenomenon. Expenditures for all categories of consumption combined have risen almost as much proportionally as have medical care expenditures, and a few categories have shown even sharper increases. In spite of the very large increase in medical care expenditures, this category accounted for only 1 percent more of the total consumption expenditures in 1955 than it did in 1941.

Gains Since 1941

For the same array of goods and services included under medical care in the 1941 study, farm families were spending $235, on the average, in 1955, as compared with $60 in 1941 (table 1). When this is converted to 1941 dollars to eliminate the effect of the price change since that year, they are found to be buying a little more than twice as much in 1955 as in 1941. Moreover, this comparison of data for families understates the change in per capita expenditure since average size of farm families decreased from 4.0 to 3.8 persons in this period.

Table 1. Main categories of medical care expenditures in current dollars and in dollars of constant purchasing power, farm-operator families and single farm operators

Expenditure category	1955		1941	1955 as a percent of 1941 computed in 1941 dollars
	In 1955 dollars	In 1941 dollars [1]		
All medical care [2]	$235	$126	$60	210
Health insurance and prepayment plans	42	13	3	433
Direct expenditures	193	113	57	198
Physicians' services [3]	63	39	22	177
Dental care [3]	29	17	9	189
Eye tests and glasses [3]	13	10	5	200
Hospital care	36	11	7	157
Medicines and drugs [2 3]	39	29	10	290
Other [3 4]	13	7	5	140

[1] Adjusted by the consumer price index (*4*). The most suitable component of the index has been applied to the individual categories of medical care expense and the total obtained by addition. Since health insurance was not included in the index in 1941, hospital care, the major component of health insurance, was used for that year.

[2] In this table, vitamin and mineral preparations, a component of medicines and drugs in the 1955 data in tables 2, 3, and 4, have been excluded to achieve comparability with the 1941 data.

[3] To achieve comparability with the 1941 data, unitemized expenditures reported on the 1955 schedules have been allocated to these items proportionately.

[4] Includes nursing care, services of other practitioners (osteopaths, naturopaths, chiropractors, faith healers, midwives), laboratory tests and X-rays, medical appliances and supplies, and ambulance service.

All the items of medical care have not shared equally in this gain. Health insurance appears to have made the greatest gain, although premiums paid cannot be measured precisely in dollars of constant purchasing power because there is no measure of the change in price of this item over the whole period. Consumption of medicines and drugs appears to have tripled. This increase is of particular interest since it might be expected that as the amount of medical care increased, there would be a decline in self-medication and therefore no more than a moderate increase in the volume of drugs bought. At least two factors have operated to increase expenditures. Dispensing of drugs by physicians has been decreasing over the past several decades, with a resulting increase in purchases. Also, the period since 1941 has been marked by the introduction of a wide range of antibiotics and other new drugs that are in a completely different price range from the old drugs. It is also possible that there was over-reporting of this item in 1955, although there is no conclusive evidence on this point.

The relative increases for the other major components of medical care were less than that for the category as a whole. If, however, instead of considering health insurance as a separate component, one-third of the premiums are assigned to physicians' services and two-thirds to hospital care, the volume of physicians' care used is found to have increased in almost the same proportion as all medical care, and the volume of hospital care to have made a greater increase.

While health insurance and medicines and drugs, the items that made large individual gains, account for more than 40 percent of the total increase, some of the items that made smaller gains also contributed substantially. Direct expenditures for physicians' services ac-

Methodology and Definitions

Data on medical expenses in 1955 were obtained as part of a survey of farm-operators' farm and family expenditures conducted jointly by the U. S. Department of Agriculture and the U. S. Bureau of the Census to provide a set of weights reflecting expenditure patterns of a recent year for use in calculating the parity index, and to improve the basis for estimating farm-operator production expenses (8). Because of the large number of items for which data were required, two national samples were used, data on production expenses being obtained from one and data on family living expenses and income from the other. In the sample providing data on family living expenses there were 3,985 families and single individuals.

In this survey, expenditures for medical care include health insurance premiums and dues to prepayment plans paid by the family, and expenses for the treatment of illness and routine physical and dental examinations incurred by the family in the schedule year and not covered by insurance. Expenses were reported even though payment may not have been made within the schedule year.

The following differences in definitions relating to medical care exist between the various studies cited here:

In the 1950 and 1955 studies, vitamin and mineral preparations are classified as medicines and drugs, hence in medical care. In the earlier studies these items were considered to be food supplements and were classed with food. Inclusion of these preparations raises the average farm-family expenditures in 1955 from $37 to $43.

Expenditures for health insurance prepayment plans were not covered in the 1935–36 study. This disparity does not affect the comparability of the data materially since there was very little of this type of insurance at that time.

More detail on medical care expenditures from this survey will be available in forthcoming publications of the Department of Agriculture.

count for a fourth of the gain; although the relative increase in this item was below the average for medical care, the item was such a large component of the total in 1941 that even a moderate percentage increase resulted in a substantial increase in the total amount. Similarly, dental care, although showing a much less dramatic rise in expenditures than did health insurance, contributed almost as much as health insurance to the overall gain.

The prices of the components of medical care did not change equally over the period 1941–55. As measured by the consumer price index of the Bureau of Labor Statistics, the cost of services increased more than the cost of goods. The greatest price increase occurred in hospital rates.

As a result of price changes and differences in the volume of services and goods consumed, there have been changes in the distribution of the medical care dollar. Physicians' services, including those paid for directly and by insurance, are still the largest single component, but they have become somewhat less important, taking only 33 cents of the medical care dollar instead of 38 cents. Dental care and eye tests and glasses also showed small losses in importance. The greatest change occurred in hospital care; the proportion of the medical care dollar spent for this item, either directly or through insurance, almost doubled.

Farm-Urban Comparisons

As was pointed out earlier, in 1950 urban families spent, on the average, $65 per person for medical care. If between 1950 and 1955 they increased their spending in proportion to the increase shown by all United States consumers (and this is a reasonable assumption since they constituted almost two-thirds of all consumers in 1950), by 1955 they were spending $81 per person. If this is so, in that year the level of spending of rural families ($63 per person) was about 80 percent of that of urban families, whereas in 1941 it was less than 50 percent. The amount of money spent is not a precise measure of the volume of services received, since there may be a price differential between urban and rural areas.

The division of the medical care dollar between health insurance and prepayment plans on the one hand and direct expenditures on the other seems to be much the same in urban and farm families, but fewer farm families have the protection of insurance. In 1950, 64 percent of urban families reported premium payments and presumably in the 5 years between surveys this proportion increased somewhat, but in 1955 only 51 percent of farm families were making such payments. The average premium paid in 1955 by farm families carrying insurance was considerably larger than the average premium paid in 1950 by urban families with insurance: $82 as contrasted with $53. Although no direct comparison of coverage obtained is possible, it is readily apparent that the covered farm family has considerably less protection than the covered urban family. The difference in premiums is barely enough to offset the price rise in the intervening years. Additional considerations are that fewer farm than urban families obtain their insurance in connection with employment and therefore fewer benefit from the contributions of employers, and that many farm families are not in a position to take advantage of group insurance plans and the savings they make possible.

Effect of Income and Other Factors

Income is an important determinant of expenditures since families cannot continuously spend beyond their resources. The expenditure data classified by income must be interpreted

Table 2. Medical care expenditures, by family income, farm-operator families and single farm operators, 1955

Region and income class [1]	All medical care		Health insurance		Direct expenditures		Percent of families having expenditures for—		Average family size	Number of families represented by sample
	Per family	Per person	Per family	Per person	Per family	Per person	Health insurance	Direct expenditures		
United States	**$240**	**$63**	**$42**	**$11**	**$198**	**$52**	**51**	**99**	**3.8**	**4,760,050**
Under $250	252	74	33	10	219	64	40	97	3.4	429,233
$250–$499	152	45	25	7	128	38	32	96	3.4	211,320
$500–$999	145	45	17	5	129	40	27	96	3.2	583,147
$1,000–$1,499	186	53	30	9	156	45	42	99	3.5	519,675
$1,500–$1,999	209	55	34	9	174	46	45	100	3.8	484,019
$2,000–$2,999	249	61	46	11	202	49	58	99	4.1	840,136
$3,000–$3,999	271	65	56	13	215	51	66	99	4.2	605,229
$4,000–$4,999	277	62	65	14	212	47	68	99	4.5	322,408
$5,000–$7,499	360	86	64	15	296	70	69	100	4.2	350,072
$7,500 and over	431	100	79	18	352	82	69	100	4.3	176,385
North Central	**241**	**65**	**48**	**13**	**193**	**52**	**56**	**100**	**3.7**	**1,686,776**
Under $1,000	214	67	28	9	187	58	37	99	3.2	383,642
$1,000–$1,499	191	62	39	13	152	49	53	99	3.1	168,071
$1,500–$1,999	205	62	40	12	165	50	49	100	3.3	192,436
$2,000–$2,999	238	63	52	14	186	49	61	100	3.8	349,944
$3,000–$4,999	264	60	64	15	200	45	68	100	4.4	364,568
$5,000–$7,499	327	73	60	13	267	59	72	100	4.5	118,045
$7,500 and over	295	72	68	17	227	55	73	100	4.1	50,502
South	**222**	**57**	**34**	**9**	**188**	**48**	**45**	**98**	**3.9**	**2,275,320**
Under $500	183	52	24	7	159	45	32	96	3.5	334,087
$500–$999	142	44	15	5	127	40	24	95	3.2	372,517
$1,000–$1,499	176	46	24	6	153	40	35	100	3.8	298,873
$1,500–$1,999	204	47	27	6	176	41	41	100	4.3	224,636
$2,000–$2,999	263	58	40	9	223	50	54	99	4.5	372,353
$3,000–$7,499	288	69	54	13	234	56	65	99	4.2	486,292
$7,500 and over	487	116	88	21	399	95	74	100	4.2	60,054

[1] Total money income as collected in this survey was subject to under-reporting, particularly for income from operation of the farm. The income distributions given here are not corrected for this under-reporting, but should nevertheless be useful for classifying families into homogeneous groups (with respect to 1955 income), for the presentation of expenditure data.

with the knowledge, however, that there was substantial under-reporting of income in this as in most surveys. Estimates of aggregate net farm income derived from the 1955 survey are as much as a third below estimates based on other data, but nonfarm income is in line with other estimates. Since the degree of under-reporting probably was not constant among all respondents, there is undoubtedly some error both in the absolute level at which some families are classified and in their relative positions in the income scale.

Average expenditures per person ranged from $45 among families reporting incomes of $250 to $1,000 to $100 among families with incomes of $7,500 and over (table 2). Families in the lowest income class (under $250) reported larger expenditures than those with somewhat higher incomes. Although it can be assumed that some of these families are misclassed as a result of under-reporting of income, it is also probable that some of them are in the lowest class because of temporary fluctuations in income. For the latter group, ill health may partly explain both their income position and the size of their medical care expenditures, but this can be only a minor factor as the same relationships can be observed in the total consumption expenditures and in those for other categories.

In the group with reported incomes under $2,000, which included almost half of all farm families, medical care expenditures averaged $55 per person or less. Those with reported incomes between $2,000 and $5,000, slightly more than a third, had per person expenditures averaging between $60 and $65. Expenditures rose rapidly among families with incomes of $5,000 or more.

At all income levels, the proportion of families reporting some direct medical care expenditures was high, with only a slight tendency to increase with income. The proportion of families reporting expenditures for health insurance was considerably lower and was more closely related to reported income, rising with it. There was less variation with income in per person expenditures in the North Central region than in the South (table 2). Average per person expenditures in families with incomes below $3,000 were lower in the South than in the North Central States, but when incomes were $3,000 or more southern families spent more per person.

Other characteristics than income are also of importance in determining expenditures. Frequently, however, these characteristics have systematic relationships among themselves and with income that make it difficult to show by means of simple tabulations such as those presented here which characteristics are most closely related to the variation. In table 3 expenditures by race, tenure, education of the operator, and family size are shown for all farm families and for families in a relatively narrow income band. In the latter group, much of the effect of variation in income is eliminated, but other internal relationships are not controlled. For example, nonwhite families are less likely to be in the owner class, they have lower educational attainment as a rule, and the families tend to be larger.

In the South, where 19 percent of all respondents were nonwhite, medical expenditures show a difference by race. In families with incomes below $3,000, who constitute 85 percent of the nonwhite and 67 percent of the white respondents, medical care expenditures of nonwhite families tended to be about half those of white families of comparable income. Since nonwhite families are larger on the average than white families, the difference was even greater on a per person basis. Interestingly enough, white and nonwhite families carried some type of health insurance in about the same proportions, but the average premium or dues payment was smaller among nonwhite families. Race had a greater effect on expenditures for medical care than on total consumption expenditures. This may result from differences in facilities available to the two groups. It may also be the indirect effect of education, for in this study medical care expenditures tended to rise with an increase in the education of the farm operator.

Two different regional patterns appear when medical care expenditures are classified by income and tenure. In the North Central region, tenants consistently spent more than owners with comparable incomes. In the South, however, owners spent more than cash-and-share

Table 3. Medical care expenditures, by selected family characteristics, farm-operator families and single farm operators, 1955

Family characteristics	United States			North Central			South		
	Total medical care	Health insurance	Direct expenditures	Total medical care	Health insurance	Direct expenditures	Total medical care	Health insurance	Direct expenditures
	All incomes								
All families	$240	$42	$198	$241	$48	$193	$222	$34	$188
Race:									
White	253	44	209	(1)	(1)	(1)	247	37	210
Nonwhite	118	23	95	(1)	(1)	(1)	117	23	95
Tenure:									
Owners and part owners	250	44	206	236	46	191	246	38	208
Tenants other than croppers	221	39	183	260	54	206	158	20	138
Sharecroppers	78	18	59	(2)	(2)	(2)	78	18	59
Education of operator (years):									
Less than 9	211	36	175	230	44	186	189	28	161
9–12	279	50	229	245	51	195	297	44	252
13 or more	323	64	259	(2)	(2)	(2)	(2)	(2)	(2)
Family size (persons):									
Less than 1.5	79	17	62	80	20	60	63	15	48
1.5–2.4	221	33	187	204	34	169	211	27	184
2.5–3.4	260	44	216	254	48	206	264	36	228
3.5–4.4	263	51	212	251	55	196	256	47	209
4.5–5.4	269	55	213	278	62	217	246	44	202
5.5–6.4	258	43	215	279	50	229	201	30	170
6.5 or more	250	44	206	311	71	240	197	30	167
	Incomes of $1,000–$1,999								
All families	$197	$32	$165	$199	$140	$159	$188	$25	$163
Race:									
White	209	33	175	(1)	(1)	(1)	210	26	184
Nonwhite	100	23	77	(1)	(1)	(1)	100	23	77
Tenure:									
Owners and part owners	207	32	174	197	35	163	206	29	177
Tenants other than croppers	177	35	142	205	56	149	141	13	128
Sharecroppers	79	13	66	(2)	(2)	(2)	79	13	66
Education of operator (years):									
Less than 9	187	29	158	181	38	143	183	22	161
9–12	214	38	176	218	40	177	206	35	171
13 or more	274	54	220	(2)	(2)	(2)	(2)	(2)	(2)
Family size (persons):									
Less than 1.5	71	19	51	55	22	33	66	15	51
1.5–2.4	194	32	161	182	36	146	195	28	168
2.5–3.4	205	34	171	219	48	171	193	20	173
3.5–4.4	253	40	213	238	45	193	263	35	228
4.5–5.4	222	42	180	218	42	176	190	32	158
5.5–6.4	183	24	159	219	35	184	161	20	141
6.5 or more	157	21	136	234	41	193	133	18	115

[1] Data not tabulated because the percentage of nonwhite operators is small. [2] Data not shown because of small number of cases.

tenants with the same incomes, and the latter in turn spent more than sharecroppers. The pattern in the North Central region seems to represent a break with the past. It may be related to the higher educational attainment of tenants in this region; they tend to be considerably younger than owners and therefore to have progressed further before they left school. It may, however, reflect current attitudes toward farm ownership and the choice between saving to invest in the farm and spending for current consumption. It is possible that the higher expenditures of tenants represent a choice on their part of higher consumption and postponement of farm ownership, and a choice on the part of the owners to build up their investment in the farm. In the South, it must be recognized that the pattern by tenure is strongly influenced by the racial pattern. The proportion of nonwhite operators is largest among sharecroppers and smallest among owners. The pattern of educational attainment is also the reverse of that in the North Central region; the higher the position on the tenure ladder, the further the group has gone in school.

For the farm population as a whole, expenditures per family increased with family size until the 3-person family was reached; they remained at a fairly constant level until the 6-person family was reached and then decreased among the largest families. This pattern, however, conceals sharp regional variation. In the North Central States the average expenditure tended to rise more or less consistently with family size throughout the entire range, while in the South it rose only until the three-person family was reached and dropped thereafter. In both regions there was a sharp increase in per person expenditures between the single individual and the two-person family; thereafter per person expenditures decreased with increase in family size.

Regional Comparisons

In 1955, medical care expenditures were lower among southern farm families than among those in the North Central region. This difference is due in part to lower income, lower educational attainment, and a higher proportion of nonwhites among the population in the South. That this is not the entire explanation, however, can be seen by comparing the expenditures of comparable groups in the two regions. At most income levels, southern families spent less than those in the North Central region (table 2). Furthermore, groups comparable as to tenure, education, or family size, in addition

Table 4. Detail of medical care expenditures, by region, farm-operator families and single farm operators, 1955

Expenditure category	Average expenditures per family			Percent of families having expenditures		
	United States	North Central	South	United States	North Central	South
All medical care	$240	$241	$222	[1]	[1]	[1]
Health insurance and prepayment plans	42	48	34	51	56	45
Direct expenditures	198	193	188	99	100	98
Hospital care	31	27	32	21	23	20
Surgeons' care	11	11	7	9	10	7
Other physicians' (M.D.) care	49	50	47	74	74	73
Osteopaths	3	5	1	6	11	2
Other practitioners	3	4	2	8	12	4
Dental care	28	30	20	54	62	46
Eye tests and glasses	12	13	10	34	39	29
Nursing care	2	1	2	2	1	2
Laboratory tests and X-rays	3	3	2	12	14	9
Medicines and drugs	43	37	46	[1]	[1]	[1]
Medical appliances and supplies	2	1	1	13	14	10
Other and unitemized medical expenses	13	11	16	[1]	[1]	[1]

[1] Not available.

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to income, show a similar regional disparity (table 3). It is encouraging to note, therefore, that since 1945 expenditures have increased more in the South than in the North Central region. This can be attributed at least in part to a greater increase in income in the South and to a more than proportionate loss from the population of those groups whose expenditures are lowest—sharecroppers, other tenants, and nonwhite operators.

For most categories of medical care southern families spent less than North Central families (table 4). Only for medicines and drugs do they appear to spend substantially more. Direct expenditures for hospital care are somewhat higher, but when that proportion of insurance premiums assignable to hospital care is added to direct expenses, the total for northern families is higher. The higher expenditures of southern families for medicines and drugs, especially when occurring in conjunction with lower expenditures for physicians' care, seem to indicate a greater degree of self-medication.

The general patterns of expenditures in the two regions were similar. Such differences as were found, in line with the difference in amount of expenditures, indicate less care in the South. Fewer southern families had expenditures for dental and eye care, and smaller proportions of the medical dollar were spent on these items. Fewer southern families had direct expenditures for hospital care, and it probably follows that there were fewer hospital admissions. If health insurance premiums are assigned to the categories of care, expenditures for both hospital care and physicians' services were of greater importance in the North Central region than in the South. Since total medical expenditures were lower in the South than in the North Central region and expenditures for medicines and drugs were greater, it follows that a considerably larger proportion of the medical dollar went for medicines and drugs in the South.

This regional disparity is not confined to the farm segment of the population. In fact, per person expenditures for medical care show that the relative position of the rural South is higher than that of the urban South:

	United States	*South*
Farm operators, 1955	$63	$57
Urban population, 1950	65	55

The urban South, however, has considerably less effect on the national average for the urban population than does the rural South on the national rural figure, since less than one-fourth of all urban families live in that region as compared with almost one-half of all rural families. If the South carried the same weight in both the urban and farm populations, much of the present difference between urban and rural expenditures would disappear.

REFERENCES

(1) U. S. National Resources Planning Board: Family expenditures in the United States. Washington, D. C., U. S. Government Printing Office, 1941.

(2) Hollingsworth, H., and Klem, M. C.: Medical care and costs in relation to family income. U. S. Social Security Board, Bureau of Research and Statistics, Memorandum No. 51. Washington, D. C., 1943.

(3) University of Pennsylvania. Wharton School of Finance and Commerce: Study of consumer expenditures, incomes, and savings. II. Summary of family expenditures for current consumption. Philadelphia, 1956.

(4) U. S. Bureau of Labor Statistics: Consumer price index, price indexes for selected items and groups, annual indexes, 1935–55, and quarterly indexes, December 1952–March 1956. Washington, D. C., July 1956, 12 pp. Processed.

(5) U. S. Agricultural Marketing Service: The farm income situation, July 1957. Washington, D. C. Processed.

(6) U. S. Department of Agriculture: Agricultural statistics, 1955. Washington, D. C., U. S. Government Printing Office, 1956.

(7) Mushkin, S.: Age differential in medical spending. Pub. Health Rep. 72: 115–120, February 1957.

(8) U. S. Bureau of the Census: Census of agriculture: 1954. Vol. III, Special reports. Pt. 11, Farmers' expenditures. Washington, D. C., U. S. Government Printing Office, 1956.

Available data indicate an increase in body fat up to about age 50, with women gaining more than men. It is suggested that "the secret to a long life for a body pleasantly surfeited with fat may be found by studying older women."

Age Changes in Body Composition

OLAF MICKELSEN, Ph.D.

EVALUATION of age changes in the composition of the body is hampered by the inadequacy of current procedures for determining body composition. Although a number of techniques have been proposed, only a few of these have been validated by direct carcass analysis. Validation has been done only on experimental animals.

In order to simplify the problem of determining body composition, the body may be said to be composed of the skeleton, fat, and fat-free tissue (muscle). For any individual, the weights of the skeleton and of fat-free tissue appear to be fixed within relatively narrow limits. The weight of body fat, however, covers a relatively wide range.

The methods used in determining body composition provide, at best, estimates of the size of either the fat or fat-free tissue. Either one or both of these components may be measured, but usually only one is determined. The mathematical equations that have been developed for computing the percentage composition of the body contain factors that make allowances for the weight of the skeleton. Minerals are one of the chief components of the skeleton, but since minerals account for a relatively small percentage of the body weight, any variation in the size of this component will have only a minor influence on body composition.

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Although it would be desirable to know the changes that occur with age in all body components, most of the work in the field of body composition has been concentrated on determination of the amount of fat. This stems from the interest engendered during the past few years in obesity in general. Changes in the skeletal mass have been largely neglected.

On the basis of clinical experience it has been proposed that changes do occur in the skeletal mass. Many clinicians working in the field of geriatrics are impressed by the fragility of the bones in their older patients. This has been assumed by some to be due to a negative calcium balance, with a consequent depletion of bone minerals. However, a recent study suggests that "the onset of bone fragility in the aged is a composite effect of many factors and is probably more intimately related to endocrine changes, decreased activity, and loss of muscle tone than to level of nutrition" (*1*).

Methods of Determining Body Composition

A brief review of some of the procedures proposed for determining body composition will give some idea of the limitations and difficulties in this field. Although there are a number of methods for estimating the composition of the body, none of them is ideal. Each procedure has its limitations. The method that has been used most frequently as a reference or standard is the densitometric technique based on weighing the individual under water.

Because of its simplicity, comparison of the individual's height and weight with values listed in standard tables is probably the most commonly used procedure for obtaining crude estimates of body fatness, and thus, indirectly, of body composition.

Standard Height-Weight Tables

The height-weight tables most often used for evaluating body fatness are those compiled by the Association of Life Insurance Medical Directors on the basis of medical examinations performed on individuals applying for insurance during the years 1885 through 1910 (*2*). One of the most serious limitations in using these tables is the absence of a correction factor for the clothing and shoes worn by the individuals who were weighed (*3*). Another limitation is the disagreement as to the deviation in weight that must occur before an individual is considered obese. Values ranging from 5 to 20 percent have been proposed as the upper range of "normal" body weight for any height.

These tables make no allowance for variation in body build. Keys and Brozek (*4*) have shown that the variation in body build could be illustrated by the data of Munro (*5*). Munro found that the groups of selective service registrants of the same age and stature who had chest circumferences of 32, 37, and 42 inches had average weights of 130, 158, and 198 pounds, respectively. In general, the heaviest men had the largest body frames; yet the height-weight tables suggested only one weight (150 pounds) for individuals of this height. When compared with the values in the table, the men with the largest body frames would be as much as 36 percent overweight. That all of the heaviest men were not obese is suggested by the work of Welham and Behnke (*6*). Using the densitometric technique (described below), they found that professional football players who were in peak physical condition were 20 or more percent overweight according to the standard height-weight tables. However, on the basis of body density, these "overweight" men had very little fat in their bodies. If obesity is defined as a condition in which there is a surplus of body fat, these men obviously were not obese.

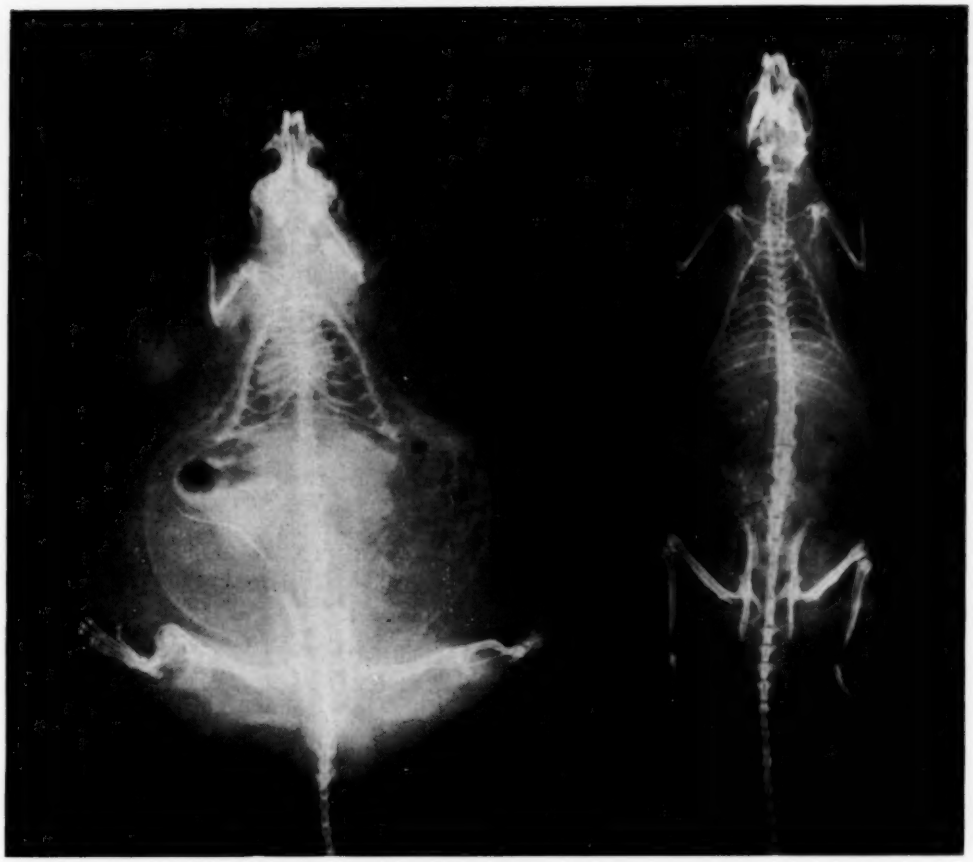
Subcutaneous Fat Determinations

Body fat has also been estimated from the thickness of skinfolds on various parts of the body. The skinfold is "lifted up" with the fingers from the underlying muscle. A variety of calipers are available for quantitating these measurements. This procedure is based on the observation that in man a large proportion of the total body fat is found in the subcutaneous tissue (*4*).

Unfortunately, there are practically no data on human beings to indicate the relative distribution of fat throughout the body in the lean and the obese. X-ray evidence is available for rats which became obese as a result of an ad libitum consumption of a high-fat diet (*7*). These rats, compared with their littermates fed a low-fat diet, showed a tremendous increase in the amount of fat in the subcutaneous area (see illustration). Associated therewith is a marked increase in the amount of fat in the abdominal cavity. The lean rat shows a proportionately smaller amount of fat, not only in the subcutaneous areas but in the abdominal cavity as well. Comparable data for guinea pigs have been presented by Pitts (*8*). The mass of the subcutaneous fat in the guinea pig was almost directly proportional to the total body fat.

The most extensive evaluation of the skinfold-thickness method for determining body fat has been made by Keys and Brozek (*4*). In their study the skinfold thickness at a number of sites on the body was determined for a large number of subjects. At the same time, total body fat in each subject was estimated by the densitometric method. On the basis of these measurements equations were developed for estimating the body fat from the skinfold thickness (*9*). Similar work has been done by Pascale and others (*10*, *11*). The equations provide values which at best only approximate the body fat content as calculated from body density. A partial explanation for the inconsistent body fat values derived from the skinfold measurements stems from the finding that there is considerable individual variation in the distribution of subcutaneous fat throughout the body (*4*).

A few attempts have been made to determine the amount of fat in the body from X-rays of



X-rays of lean and obese littermate rats.

selected areas. Stuart and co-workers (*12*, *13*) have used X-rays of the antero-posterior view of the right leg at the maximal width of the calf. These studies were confined largely to children. Reynolds (*14*) has extended this technique to the study of adults. He reported that the ratio of thickness of adipose tissue to bone width of the leg is much greater in women than in men. The ratio decreases with age in men but increases in women.

A recent report by Garn (*15*) on the fat content of adults as determined by X-rays suggests that there is very little difference in the absolute amount of fat in men and women. Since the body weights of the women were considerably lower than those of the men (58.3 as compared with 76.4 kilograms), the percentage differences in fat content were significant. Garn found that the average weight of fat in 107 healthy American women ranging in age from 20 to 60 years, with a mean of 39 years, was 13.7 kilograms, while that in 81 men in the same age range was 12.6 kilograms. The fat content of the women was 23.7 percent, for the men 16.8 percent.

Densitometry

A procedure that has been studied rather extensively during the past few years determines body density and, from this, the relative composition of the body. The difference in density of body fat and the fat-free residue is great enough to permit calculating the amount of fat in the body from the body's density. This density has been determined by two different methods.

One method of determining body density is based on weighing the subject under water. This procedure received its greatest stimulation as a result of the studies of Behnke and coworkers (*16*). The technique is fraught with difficulties. The primary one is the inability of readily determining the residual air and the air that may be retained in the gastrointestinal

tract at the time of the underwater weighing. Body density can be corrected for residual air, but to do it accurately would make the determination both cumbersome and time-consuming. A standard correction cannot be made for residual air since there is considerable variation among individuals, as well as an increase in the absolute residual air volume with increasing age (*4*). A second difficulty is trying to weigh under water an individual who has any fear of being submerged. The latter is likely to be important with older people, especially those who have never learned to swim.

The other method for determining body density involves measurement of the body's volume. The volume of the body can be calculated by the displacement of helium in a chamber of known volume. This method has been used by Siri (*17*) for human beings and by Walser and Stein (*18*) for animals.

Theoretically, the gas-displacement technique should be far superior to the underwater-weighing procedure since any air in the lungs at the time of measurement should have practically no influence on the density. The anxiety associated with the method should be minimal. To what extent this modification of the densitometric method will be used is at present hard to predict.

Wedgewood and Newman (*19*) modified the Drinker respirometer so that the volume of the subject can be calculated from the changes in pressure associated with the pulsations of the bellows. The sensitivity and applicability of this technique have yet to be assayed.

Body Water

There are many data showing that in normal animals the relation between the amount of water and the amount of protein is fairly constant (*20*). The fat-free weight of the body can be calculated on the basis of this relationship. Since the minerals represent only a small fraction of the body (*21*, *22*), slight variations in this component have a negligible effect on the results. The difference between the body weight of the individual and the calculated value for fat-free body tissue represents the weight of body fat.

A number of substances, such as urea, thiourea, deuterium oxide, tritium oxide, antipyrine, and acetylaminopyrine, have been used in estimating body water. (For discussion of the various techniques and references thereto, see reference 4). A known amount of the substance is given by mouth (urea) or injected intravenously (the other substances). Blood samples are taken at intervals and analyzed for concentration of the injected substance. Total body water content can be calculated from the concentration of the substance in the blood at the different time intervals and the amount of the substance given. All the methods require from 1 to 3 hours for uniform distribution of the compound throughout the body water. The procedures necessitate all the care and safety precautions used in any intravenous therapy.

There are a number of situations in which the relationship between body water and protein deviates from the usual ratio. In most of these cases, especially those associated with edema, the abnormality is due primarily to a marked increase in the extracellular fluid. By determining the volume of the extracellular fluid as well as total body water, a correction can be made for the abnormal hydration. Recent work indicates that the extracellular fluid space as measured with thiocyanate decreases steadily from a little more than 40 percent in infancy to a constant value of 23 percent in adulthood (*23*).

Fat Solvents

Cyclopropane has been used at New York University for estimating the amount of fat in the body directly in studies with rats (*24*). The air the animal inhales contains a known amount of cyclopropane. The volume of gas retained in the body is proportional to the amount of fat in the body. So little has been done with this procedure, however, that it is difficult to evaluate its applicability and usefulness in studies with man.

Factors Influencing Body Composition

There is surprisingly little factual information on the changes that occur in the human body as it grows older. All of the studies have compared young individuals with older people. Since so many years separate a man's youth

from his old age, it is doubtful whether there will ever be any extensive longitudinal studies on adults to bridge the present gap.

Influence of Age

The height-weight tables of the Association of Life Insurance Medical Directors indicate that a half century ago both men and women continued to increase in weight even though there was no change in height as they became older (*2*). Changes comparable to these are still occurring. Recent data show that from age 25 to 60 years men in the United States who are 67 inches tall gain 8 percent in weight, while women of the same ages who are 63 inches tall gain 15 percent (*25–27*).

It has frequently been assumed that the increase in body weight with age is primarily, if not solely, due to an increase in body fat. Evidence for this assumption has been presented by Brozek (*28*), who compared a group of young men (18–25 years) with older men (45–54 years). Although the average heights for the two groups were the same, the older men were, on an average, 11 pounds heavier than the younger men. Underwater weighings corrected for residual air at the time the weights were recorded showed that the younger men had 14 percent fat in their bodies while the older men had 24 percent.

The increase in body fat associated with the increase in body weight that accompanies the aging process is accentuated by the apparent replacement of a certain portion of muscle mass with fat, according to evidence adduced by Brozek (*28*). Thirty-three young men (22 through 29 years) and an equal number of older men (48 through 57 years) were matched for height and weight. Specific gravities indicated that although there was no difference in height or weight between the two groups, the younger men had 16 percent fat in their bodies while the older men had 23 percent.

Influence of Activity

Physical activity, especially if it is strenuous, is associated with a marked reduction of body fat even though the body weight may be considerably in excess of the "standard" as listed in height-weight tables. Welham and Behnke (*6*) emphasized this point in their studies with younger men. Brozek (*28*) and Brozek and Keys (*29*) found a similar situation among older men. The physically active men were seven pounds heavier than the inactive men even though the heights were the same in both groups. However, the heavier body weights were associated with a lower body fat content (24 percent as compared with 27 percent).

Males vs. Females

Garn and Harper (*30*) have studied the distribution of fat in males ranging in age from 20 to 69 years by means of roentgenograms. Thickness of the subcutaneous fat over the iliac crest showed the greatest increase with age. Fat in the trochanteric and deltoid regions also increased, but to a lesser extent than that in the iliac region. There were no measurable changes in the thickness of the adipose tissue on the anterior surface of the leg and the middle area of the lower arm. On the basis of the amount of fat in the trochanteric area, Garn and Harper estimated that the body fat increased from 16 percent in younger men to 22 percent in older men. These values are similar to those reported by Brozek (*28*).

For women the total body fat increased from 26 percent at age 25 to 38 percent at age 55, as shown in the tabulation. These values were for women whose body weights were, on an average, from 95 to 97 percent of those listed in the standard height-weight tables (*31*). When these values are compared with those for men equally lean according to the standard height-weight tables, it is obvious that the body fat content of women is much greater than for men at each age group.

Age (*years*)	*Total body fat* (*percent*)	
	Men	*Women*
25	13.1	26.5
35	17.3	30.5
45	21.6	34.5
55	25.9	38.5

NOTE: Percentages were calculated using a linear prediction equation based on the least square fit of the values obtained by the densitometric method corrected for residual air (*31*).

In women, the increase in body fat with age is associated with an increase of the fat in the abdominal area (*32*). Since this conclusion

was based on skinfold measurements, it was not possible to determine whether the increase in inner fat was due to the fatty infiltration of the organs. There was little change in the skinfold thickness of the extremities with age in women, but there were marked changes in the thickness of subcutaneous fat on the chest, side, waist, and back.

Edwards (*33*) determined the skinfold thickness in 53 areas of the body in males and females ranging in age from 5 to approximately 50 years. He found that the distribution of fat in the different parts of the body was the same in both sexes before puberty. After puberty, women had about 1.2 times as much fat on their legs, in proportion to the total amount of subcutaneous fat, as men. In all groups, the women had approximately 1.7 times as much fat in the subcutaneous areas as the men. It is difficult to determine from these data any absolute changes that occur with age.

Conclusion

Factual data on body composition are notably scarce. What we have indicate an increase in body weight up through approximately age 50 and a decrease thereafter (*28*). There are no data which indicate that the weight of the individual decreases after age 55.

The difficulty with the reported body weights of older people is the impossibility of determining whether the decrease in weight is due to the earlier deaths of the heavier individuals or represents an actual loss of weight with age. Although there is an increasing body of data from longitudinal studies of children, such information is woefully lacking for adults, especially for individuals over 60 years of age. Only longitudinal studies permit determination of the actual changes that occur with age.

Few studies bear upon changes in body composition occurring in women with the passage of time. The prominent attention that obesity has received during the past few years would make such studies desirable. The work of Skerjl and others (*32*) indicates that in older women of "standard" weight, more than one-third of their body is fat. Even under that "stress," if it is stress, women outlive men by a significant number of years. This suggests that the secret to a long life for a body pleasantly surfeited in fat may be found by studying older women.

REFERENCES

(*1*) Hayes, C. B., Bowser, L. J., and Trulson, M. F.: Relation of dietary intake to bone fragility in the aged. J. Gerontol. 11: 154–159 (1956).

(*2*) Association of Life Insurance Medical Directors: Medico-actuarial mortality investigations. New York, N. Y., 1912, vol. 1.

(*3*) Rion, J. W.: The development of height-weight tables from life insurance data. Washington, D. C., U. S. Public Health Service Division of Chronic Disease and Tuberculosis, 1952. Manuscript.

(*4*) Keys, A., and Brozek, J.: Body fat in adult man. Physiol. Rev. 33: 245–325 (1953).

(*5*) Munro, E. H.: Preparation of anthropometric monographs. U. S. Office of the Quartermaster General Environmental Protection Branch Rep. No. 184. Lawrence, Mass., Climatic Research Laboratory, 1952.

(*6*) Welham, W. C., and Behnke, A. R.: The specific gravity of healthy men. Body weight ÷ volume and other physical characteristics of exceptional athletes and of naval personnel. J. A. M. A. 118: 498–501 (1942).

(*7*) Mickelsen, O., Takahashi, S., and Craig, C.: Experimental obesity. I. Production of obesity in rats by feeding high-fat diets. J. Nutrition 57: 541–554 (1955).

(*8*) Pitts, G. C.: Gross composition of fat-free mammalian body (abstract). Federation Proc. 10: 105 (1951). (Quoted by Behnke and others, reference 20.)

(*9*) Brozek, J., and Keys, A.: The evaluation of leaness-fatness in man: Norms and interrelationships. Brit. J. Nutrition 5: 194–206 (1951).

(*10*) Pascale, L. R., Grossman, M. I., and Sloane, H. S.: Correlation between thickness of skinfolds and body density in 88 soldiers. U. S. Office of the Surgeon General, Army, Medical Nutrition Laboratory Rep. No. 162. Denver, Colo., Fitzsimons Army Hospital, 1955.

(*11*) Pascale, L. R., Grossman, M. I., Sloane, H. S., and Frankel, T.: Correlations between thickness of skinfolds and body density in 88 soldiers. Human Biol. 28: 165–176 (1956).

(*12*) Stuart, H. C., and Dwinell, P. H.: Growth of bone, muscle, and overlying tissue in children six to ten years of age as revealed by roentgenograms of the leg area. Child Development 13: 195–213 (1942).

(*13*) Stuart, H. C., Hill, P., and Shaw, C.: Growth of bone, muscle, and overlying tissue as re-

vealed by studies of roentgenograms of the leg area. Monogr. Soc. Res. Child Development 5: 1–190 (1940).

(14) Reynolds, E. L.: The fat-bone index as a sex-differentiating character in man. Human Biol. 21: 199–204 (1949).

(15) Garn, S. M.: Fat weight and fat placement in the female. Science 125: 1091–1092, May 31, 1957.

(16) Behnke, A. R., Feen, B. G., and Welham, W. C.: The specific gravity of healthy men. Body weight divided by volume as an index of obesity. J. A. M. A. 118: 495–498 (1942).

(17) Siri, W. E.: Fat, water, and lean tissue studies (abstract). Federation Proc. 12: 133 (1953).

(18) Walser, M., and Stein, S. N.: Determination of specific gravity of intact animals by helium displacement. Comparison with water displacement. Proc. Soc. Exper. Biol. & Med. 82: 774–777 (1953).

(19) Wedgewood, R. K., and Newman, W. N.: Measurement of body fat by air displacement. Am. J. Phys. Anthropol. 11: 260 (1953).

(20) Behnke, A. R., Osserman, E. F., and Welham, W. C.: Lean body mass: Its clinical significance and estimation from excess fat and total body water determination. A. M. A. Arch. Int. Med. 91: 585–601 (1953).

(21) Forbes, R. M., Cooper, A. R., and Mitchell, H. H.: The composition of the adult human body as determined by chemical analysis. J. Biol. Chem. 203: 359–366 (1953).

(22) Mitchell, H. H., Hamilton, T. S., Steggerda, F. R., and Bean, H. W.: The chemical composition of the adult human body and its bearing on the biochemistry of growth. J. Biol. Chem. 158: 625–637 (1945).

(23) Fellers, F. X., Barnett, H. L., Hare, K., and McNamara, H.: Changes in thiocyanate and sodium spaces during growth. Pediatrics 3: 622–628 (1949).

(24) Lesser, G. T., Blumberg, A. G., and Steele, J. M.: Measurement of total body fat in living rats by absorption of cyclopropane. Am. J. Physiol. 169: 545–553 (1952).

(25) Hundley, J. M.: Diabetes—Overweight: U. S. Problems. J. Am. Dietet. A. 32: 417–421 (1956).

(26) Swanson, P., Roberts, H., Willis, E., Pesek, I., and Maris, P.: Food intake and body weight of older women. *In* Weight control, edited by E. S. Eppright, P. Swanson, and C. A. Iverson. Ames, Iowa, Iowa State College Press, 1955, pp. 80–96 (84).

(27) Lowe, C. R., and Gibson, J. R.: Changes in body weight associated with age and marital status. Brit. M. J. No. 4946: 1006–1008 (1955).

(28) Brozek, J.: Changes of body composition in man during maturity and their nutritional implications. Federation Proc. 11: 784 (1952).

(29) Brozek, J., and Keys, A.: Relative body weight, age and fatness. Geriatrics 8: 70–75 (1953).

(30) Garn, S. M., and Harper, R. V.: Fat accumulation and weight gain in the adult male. Human Biol. 27: 39–47 (1955).

(31) Brozek, J., Chen, K. P., Carlson, W., and Bronczyk, F.: Age and sex differences in man's fat content during maturity. Federation Proc. 12: 21–22 (1953).

(32) Skerjl, B., Brozek, J., and Hunt, E. E., Jr.: Subcutaneous fat and age changes in body build and body form in women. Am. J. Phys. Anthropol. 11: 577–600 (1953).

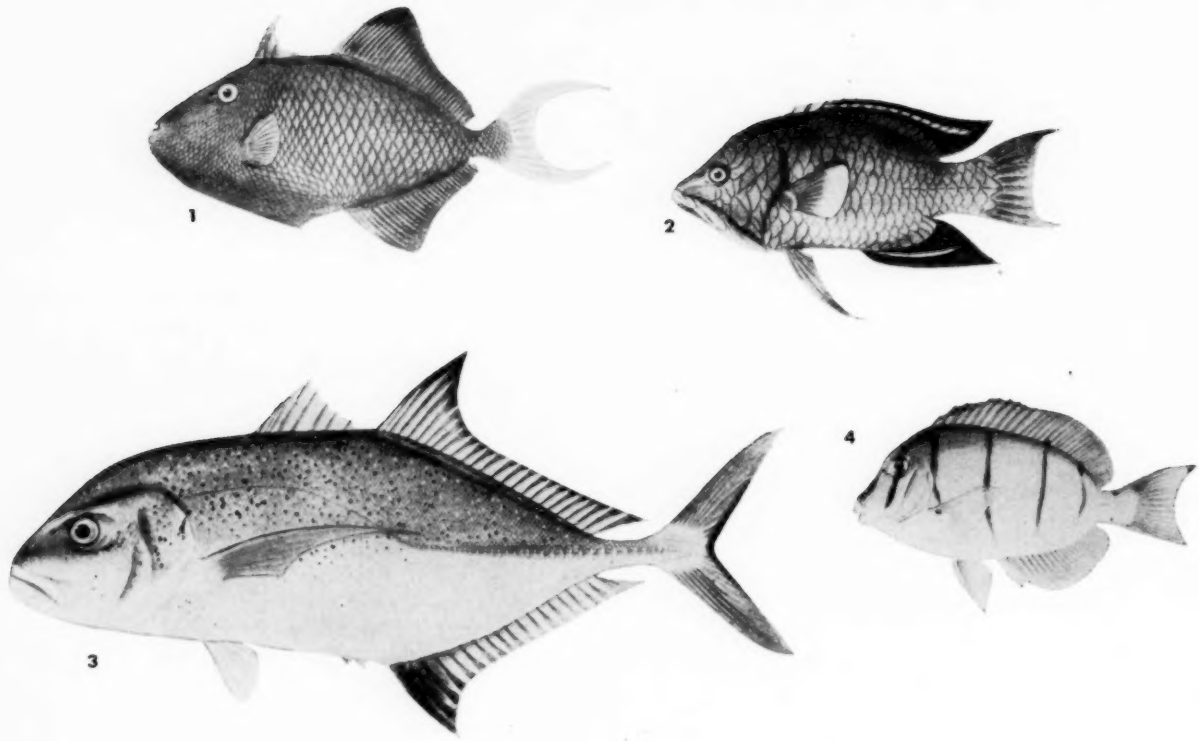
(33) Edwards, D. A. W.: Differences in the distribution of subcutaneous fat with sex and maturity. Clin. Sc. 10: 305–315 (1951).

Course in Control of Foodborne Diseases

A multidiscipline course in epidemiology and control of foodborne diseases will be offered at the Communicable Disease Center, Public Health Service, Atlanta, Ga., May 19–23, 1958.

The course is designed for physicians, veterinarians, nurses, nutritionists, dietitians, laboratory workers, environmental health supervisors, and other members of the public health team. Preference will be given to persons whose work concerns application of epidemiological techniques in this field.

Further information and application forms may be obtained from the Chief, Communicable Disease Center, Public Health Service, 50 Seventh Street, NE., Atlanta 23, Ga. Attention: Chief, Training Branch.



Poisonous Fishes

BRUCE W. HALSTEAD, M.D.

MAN'S KNOWLEDGE of poisonous fishes dates back to ancient times. At least one of the Mosaic laws is believed to have been aimed directly at eliminating poisonous fishes from the Israelite diet, "These ye shall eat of all that are in the waters: all that have fins and scales shall ye eat: And whatever hath not fins and scales ye may not eat: it is unclean unto you" (Deuteronomy 14: 9–10). The French archeologist Claude Gaillard reported that hieroglyphics and figures of the deadly *Tetraodon lineatus* appear frequently on ancient Egyptian tombs (*1*), and according to the Egyptologist Keimer, this scaleless species was recognized as poisonous during the time of the Pharaohs. Galen is said to have reported in his De Alimentis that the flesh of the moray is dangerous to eat (*2*). Alexander the Great forbade his soldiers to eat fish during conquests because he believed that some species produced skin disorders.

Peter Martyr, the first historian of the West Indies, made the earliest reference to ciguatera in 1555 (*3*). In de Landa's famous Relacion de Las Cosas de Yucatan, written in 1566, the lethal qualities of puffers are mentioned (*4*).

Beginning with the 19th century, hundreds of publications appeared on the subject of fish

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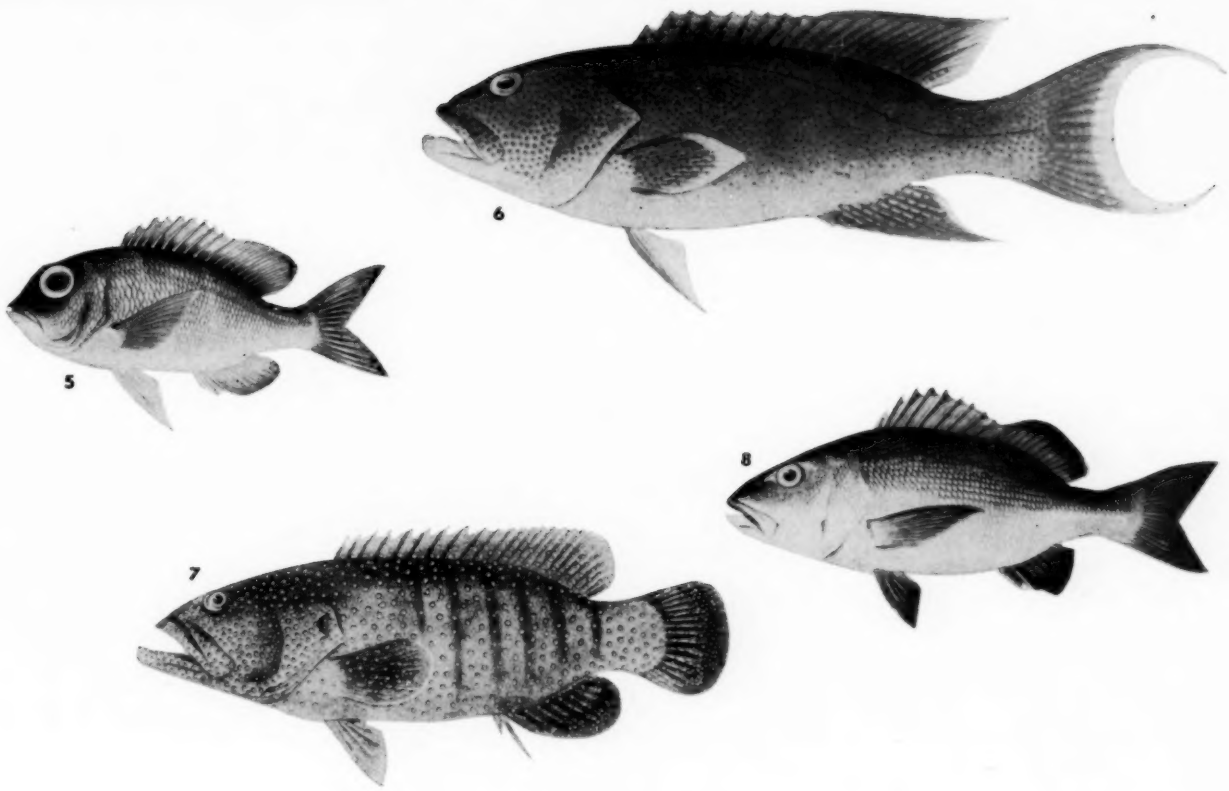

poisoning, including some comprehensive reviews and bibliographies (*3*, *5–11*).

Because of their somewhat sporadic and unpredictable appearance, generally affecting only small numbers of persons at any one time, poisonous fishes have not attracted a great deal of attention in medical circles. However, the public health significance of poisonous fishes was pointed up in the series of outbreaks which occurred in Midway, Johnston, and the Line Islands, beginning about 1943 and reaching a peak about 1946 (*12*, *13*).

Recent mass intoxications in the western Pacific have once again directed attention to the public health importance of poisonous marine organisms. These outbreaks began about 1952, became increasingly severe during 1955, and have continued until the present time, intoxicating a number estimated at more than 40,000 persons. The bulk of the outbreaks have taken place in Japan, the Philippine Islands, and more recently in Viet Nam. The causative agents were octopus, *Octopus vulgaris*, *O. döfleini*, squid, *Omnastrephes sloani pacificus*, Japanese horse mackerel, *Trachurus japonicus*, common Japanese mackerel, *Scomber japonicus*, flying fish, *Prognichthys agoo*, and oceanic bonito, *Katsuwonus pelamis*. All of the outbreaks have been seasonal, taking place during June to the middle of September. Bacteriological tests have been negative, and the degree of freshness of the organisms seems to have no bearing on the matter. The symptoms are similar to those produced by bacterial food poisoning, but no human pathogens have been isolated by Japanese epidemiologists. The mortality rate in the largest series of Japanese fish outbreaks in 1955 was 0.77 percent (*14*).

According to a report received from the Bureau of Fisheries of the Philippine Government, another series of outbreaks of fish poison-

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Some fishes associated with ciguatera are illustrated across the top of these pages. They are: **1.** Triggerfish, *Odonus niger*. **2.** Wrasse, *Epibulus insidiator*. **3.** Jack, *Caranx melampygus*. **4.** Surgeonfish, *Acanthurus triostegus*. **5.** Snapper, *Monotaxis grandoculis*. **6.** Seabass, *Variola louti*. **7.** Grouper, *Cephalopholis argus*. **8.** Red Snapper, *Lutjanus vaigiensis*.

ing took place in April 1957. The complete number of persons involved has not been determined as yet, but several deaths have been reported. The causative agent in most of the Philippine poisonings has been the oceanic bonito, *K. pelamis*. Philippine public health authorities are establishing regulations prohibiting the sale of the oceanic bonito in some localities. Some intoxications from fishes have been reported in Viet Nam, but as yet no details are available as to the nature of the outbreaks.

Since intoxications resulting from poisonous fishes are frequently confused with a variety of other ailments, a review of the epidemiological and clinical aspects of the problem of ichthyosarcotoxism is timely. The chemistry of these poisons has been reviewed elsewhere (*31*).

Epidemiology

Judging from the public health and toxicological reports that have appeared to date, any marine fish can under certain circumstances become poisonous as a result of its food habits. Toxicity is not species specific, except possibly in puffers or tetraodontoid fishes. More than 300 species of marine fishes have been incriminated as causative agents in producing human intoxications of the ciguatera type alone. Most poisonous fishes are shore forms rather than oceanic inhabitants. Fishes captured in deep waters far from shore are generally safe to eat. Some of the more common families of marine fishes which have caused human intoxications are listed under the various clinical types of fish poisoning.

Poisonous fishes are largely circumtropical in distribution, but on occasion occur in temperate waters. With the exception of 2 or 3 boreal species they are currently believed to have a maximum distributional range of 45° north and 45° south of the Equator. Particularly large populations of poisonous fishes are known to occur in the central Indo-Pacific area and in the West Indies. They are more common near islands than along continental shores. Within these general areas, poisonous fishes seem to be quite circumscribed in distribution. They may vary considerably in their distribution about a single island. A species may be toxic in one part of the island, but edible in another. Lagoon fishes are more likely to be poisonous than those living on seaward reefs.

The toxicity of puffers or tetraodontoid fishes generally follows closely their reproductive cycle. The toxin content of the fish is greatest just prior to spawning. For most puffers, spawning takes place during late spring or early summer. Toxin content is lowest during fall and winter. There is some evidence that the barracuda (*Sphyraena* spp.) may follow a similar, but less pronounced, seasonal pattern. However, in most other species there is no evidence of a seasonal fluctuation.

The poison in tetraodontoid fishes is usually more concentrated in the liver, gonads, and skin, but other parts of the viscera may also be toxic. Puffer musculature is generally nonpoisonous. The distribution of poison is exceedingly variable in other kinds of fishes. If a fish is toxic, the musculature will be found to be poisonous in about 50 percent of the specimens, and the viscera, in about 90 percent or more. However, the distribution of the poison in the body of the fish varies from one individual to the next.

No consistent pattern has been observed as to the relationship between the size of the fish and its toxicity. It has been observed that unusually large specimens of jacks (*Caranx* spp.), grouper (*Epinephelus* spp.), and barracuda (*Sphyraena* spp.) are more likely to be toxic than smaller specimens. This has not been found to be necessarily true in other species.

Aboriginal peoples have numerous methods by which they attempt to distinguish a poisonous fish from an edible one. The significance of color change in silver coins, color of the fish, condition of the gills, position of the scales, ad infinitum, is generally without scientific foundation. To the best of our knowledge, one cannot detect a poisonous fish by its appearance. The most reliable field method is to feed a small sample of the fish to a kitten or a dog. If the animal remains asymptomatic for 12 hours, the fish is generally safe to eat. Investigations are currently in progress at the School of Tropical and Preventive Medicine, Loma Linda, Calif., with the hope of developing a reliable rapid chemical field test.

Origin of the Poison

The origin of ichthyosarcotoxins in nature has been the subject of much speculation and folklore. Numerous theories have been propounded, but few have any scientific basis (*15*, *16*). It is certain, with the single exception of scombroid poison, the poisons are not bacterial in origin. Putrefactive processes do not play a part in the production of fish poisons. There is no evidence of any relationship between the presence of ichthyosarcotoxins and radioactive substances in the water. It is believed that most of these poisons are derived from the food which the fish eats. Food probably plays an important role in the direct production of even puffer poison.

The most widely accepted theory propounds the idea that the toxic substances, or their precursors, are obtained directly from marine littoral algae. It is doubtful that plankton play any role in the mechanism. Herbivores feed on the plants. Carnivores feed on the herbivores and man may become poisoned from eating either of them. Stomach content analyses have revealed that algae are more frequently present in poisonous fishes than any other types of food (*17*), and toxicological tests of these algae have shown some of them to contain toxic substances (*18*). Moreover, controlled laboratory feeding tests demonstrate that it is possible to induce toxicity in carnivorous species without evidence of detrimental effects on the fish, by feeding them toxic fish flesh. Further chemical and stomach analyses will be required before the toxin-food chain theory can be definitely established. Experimental work in attempting to determine the origin of fish poisons in nature is currently in progress by the author.

The incidence of fish poisoning cannot be accurately determined since the disease is frequently misdiagnosed and generally unreported. In the past, several hundred cases of puffer poisoning were reported each year in Japan, during some years accounting for as much as 44 percent of all fatal cases of food poisoning in that country. Japanese public health authorities state that puffers continue to be their greatest single cause of food fatalities (*19*, *20*). Probably the second most common type of fish poisoning is ciguatera. Third on the list would be scombroid poisoning, with the other forms of fish poisoning being relatively uncommon. It is unfortunate that there are so few reliable statistical data available. Local public health authorities should encourage the reporting of outbreaks, since poisonous fish may constitute a serious public health and economic threat in some regions.

Recent biotoxicological surveys that have been conducted in the tropical Pacific give some idea as to the incidence of poisonous fishes in specific localities.

Locality	*Number species tested*	*Percent of species found toxic*
Phoenix Islands (*16*)	93	29
Johnston Island (*16*)	60	75
Galapagos Islands (*29*)	57	67
Cocos Island (*30*)	33	67

Among important field studies (*7*, *8*, *21–23*), Hiyama's work (*7*) is particularly useful, magnificently illustrated, and contains a valuable review of the poisonous fish problem in Saipan and the Marshall Islands. Only meager statistical data are contained in any of these reports, but they do aid in developing an appreciation of the scope of the problem in the regions discussed.

Clinical Characteristics

Since the chemical characteristics of fish poisons have not been defined, poisonous fishes may be tentatively classified on the basis of their phylogenetic relationships and symptomatology of the intoxications which they produce (*10*, *24*). Certain fish groups are classified under more than one category. Although the weaknesses of this somewhat artificial system are recognized, it appears to be the most practical classification at present. Forms of ichthyosarcotoxism caused by fishes may be subdivided into the following clinical categories (see table).

Lamprey and Hagfish Poisoning

The slime and flesh of certain lampreys and hagfishes are reported to produce a gastrointestinal upset (*32*). The clinical characteris-

Diagnostic characteristics of the various types of ichthyosarcotoxism

Type of poisoning	Causative fish	Symptomatology
Lamprey or hagfish	Lampreys, hagfish (slime, flesh).	Gastrointestinal upset(?). Precise symptomatology unknown.
Elasmobranch	Sharks, rays (liver, flesh)	Gastrointestinal symptoms predominate in mild cases; neurological symptoms in severe cases. Deaths reported, but case fatality rate unknown.
Chimaeroid	Chimaeroid or ratfish (flesh, viscera).	Neurological symptoms(?). Precise symptomatology unknown.
Gymnothorax or moray eel.	Moray eels (flesh, viscera)	Violent neurotoxic symptoms with convulsions and paralysis predominating. Case fatality rate about 10 percent or more.
Scombroid	Scombroid fishes—tuna, bonito, skipjack, etc. (inadequately preserved flesh).	Histamine-like reaction with nausea, vomiting, flushing of the face, swelling of the lips, urticaria, and pruritus. Symptoms subside usually within 12 hours. Antihistaminic drugs effective.
Puffer	Tetraodontoid or puffer-like fishes (viscera).	Rapid onset and extremely violent neurotoxic symptoms: paresthesias, motor paralysis, convulsions, death by respiratory paralysis. Case fatality rate about 61 percent.
Ciguatera	More than 300 species of tropical reef fish, including snapper, seabass, grouper, barracuda, wrasse, parrotfish, and surgeonfish.	Onset may be gradual or sudden. Symptoms mild to severe. Gastrointestinal and neurotoxic. Paresthesias, extreme weakness, joint aches, myalgia and paradoxical sensory disturbance predominate. Case fatality rate about 7 percent.
Gempylid diarrhea	Gempylids, escolars (flesh)	Diarrhea develops rapidly but is painless. No other untoward effects.

tics of the intoxication, termed lamprey and hagfish poisoning, have not been completely defined.

Elasmobranch Poisoning

The most severe cases of elasmobranch poisoning usually result from the ingestion of the liver of sharks and rays. The musculature of some elasmobranchs is also reported as mildly toxic with the symptoms seldom more than that of a mild gastroenteritis with a predominating diarrhea. Ingestion of toxic liver results in the onset, usually within a period of 30 minutes, of nausea, vomiting, diarrhea, abdominal pain, headache, a rapid, weak pulse, malaise, cold sweats, oral paresthesia, a burning sensation of the tongue, throat, and esophagus. As time progresses, the neurological and other symptoms become more pronounced, resulting in extreme weakness, trismus, muscular cramps, sensation of heaviness of the limbs, blepharospasm, dilatation of pupils, hiccups, visual disturbances, joint aches, delirium, ataxia, incontinence, dysuria, respiratory distress, coma, and death. The recovery period, if the victims recover, varies from a day or two to several weeks. The mortality rate is not known.

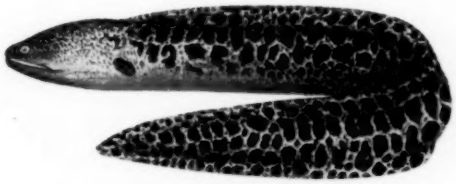
Chimaeroid Poisoning

The musculature and viscera of certain chimaeroids or ratfish have been incriminated as containing a neurotoxin. This form of ichthyosarcotoxism, if it occurs, would be termed chimaeroid poisoning. Only vague references have appeared in the literature regarding the toxicity of this group of fish, by Pellegrin in 1899, and by Phisalix in 1922. Halstead and Bunker reported in 1952 that the reproductive organs were toxic. Nothing is known about the nature of the toxin, or its relationship to other forms of ichthyosarcotoxism.

Moray Eel Poisoning

The musculature and viscera of some of the tropical marine muraenid or moray eels con-

tain a violent poison. The disease is termed gymnothorax or moray eel poisoning (*25*, *26*). Symptoms of tingling and numbness about the lips, tongue, hands, and feet, with a feeling of heaviness in the legs, usually develop within several minutes to 8 hours after ingestion of the toxin. These symptoms may be followed by nausea, vomiting, diarrhea, abdominal pain, malaise, metallic taste, sore throat, laryngeal paralysis, meningismus, laryngeal spasm, aphonia, excessive mucus production, foaming at the mouth, intense perspiration, increased body temperature, crying out as if in pain, conjunctivitis, paralysis of the respiratory muscles, ataxia, general motor incoordination, trismus, violent clonic and toxic convulsions, abnormal deep and superficial reflexes, coma, and death. Sensory reactions to deep and superficial pain are usually normal. Characteristic signs of this form of intoxication appear to be the absence of thoracic respiration with pronounced abdominal breathing, profuse perspiration, violent convulsions, purposeless movements, and the extended period of time



Moray eel, *Gymnothorax javanicus*

in which areflexia is present. In some cases the reflexes may be absent for a period of 2 months or more. The case fatality rate is estimated to be about 10 percent, and death is believed to be the result of respiratory paralysis.

Scombroid Poisoning

Some of the scombroids (tuna, skipjack, and bonito) may on rare occasions cause ciguatera, but usually they produce an entirely different form of intoxication, termed scombroid poisoning. This is the only type of fish poisoning in which bacteria appear to play an etiological role in the formation of the toxin. If scombroids are inadequately preserved, a toxic "histamine-like" substance is formed, possibly from the decarboxylation of histidine, a normal constituent of fish flesh. Kawabata and associates have recently termed this substance "saurine" (*33*). Victims complain of fish having a "sharp or peppery" taste. The symptoms most often present are nausea, vomiting, flushing of the face, intense headache, epigastric pain, burning of the throat, difficulty in swallowing, thirst, pruritus, swelling of the lips, and urticaria, which are typical of a histamine reaction. Symptoms generally subside within 12 hours.

Tuna, *Neothunnus macropterus*

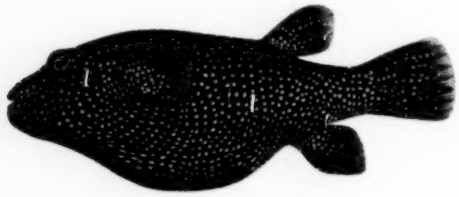
For some unknown reason scombroid fish appear to be more prone to producing intoxications of this type than other fish. The mortality rate is unknown.

Puffer Poisoning

The most violent form of fish poisoning is produced by tetraodontoid or puffer-like fishes. The disease is characterized by rapidly developing, violent symptoms. The onset and symptoms in puffer poisoning vary according to the person and the amount of poison ingested. However, malaise, pallor, dizziness, paresthesias of the lips and tongue, and ataxia most frequently develop within 10 to 45 minutes after ingestion of the fish, but cases have been reported in which the symptoms did not develop for 3 hours or more. The paresthesias which the victim usually describes as a "tingling or prickling sensation" may subsequently involve the fingers and toes, then spread to other portions of the extremities, and gradually develop into severe numbness. In some cases the numbness may involve the entire body, in which instance the patients have stated that it felt as though their bodies were "floating." Hypersalivation, profuse sweating, extreme weakness, precordial pain, headache, subnormal temperatures, decreased blood pressure, and a rapid, weak pulse usually appear early in the succession of symptoms.

Gastrointestinal symptoms of nausea, vomiting, diarrhea, and epigastric pain are sometimes present early in the disease, whereas in other cases they are totally lacking. Contradictory statements appear in the literature relative to pupillary changes, but these differences can probably be resolved on the basis of the time at which the examination is made. Apparently the pupils are constricted during the initial stage and later become dilated. As the disease progresses the eyes become fixed and the pupillary and corneal reflexes are lost.

Shortly after the development of the paresthesias, respiratory symptoms become a prominent part of the clinical picture. Respiratory distress, increased rate of respiration, movements of the nostrils, and diminution in depth of respiration are generally observed. Respiratory distress later becomes very pronounced, and the lips, extremities, and body become intensely cyanotic. Petechial hemorrhages involving extensive areas of the body, blistering, and subsequent desquamation have been reported. Severe hematemesis has also been known to occur. Muscular twitching, tremor,



Puffer, *Arothron meleagris*

and incoordination become progressively worse and finally terminate in an extensive muscular paralysis. The first areas to become paralyzed are usually the throat and larynx, resulting in aphonia, dysphagia, and later complete aphagia. The muscles of the extremities become paralyzed and the patient is unable to move.

As the end approaches, the eyes of the patient become fixed and glassy, and convulsions may occur. The victims may become comatose, but in most instances they retain consciousness and their mental faculties remain acute until shortly before death. Death results from a progressive ascending paralysis involving the respiratory muscles. On the basis of Japanese statistics, the case fatality rate is 61.5 percent. If death occurs, it generally takes place within the first 6 hours, or within 24 hours at the latest. The prognosis is said to be good if the patient survives for 24 hours.

Ciguatera

More than 300 species of marine fish have been incriminated as causative agents of this form of ichthyosarcotoxism. Fish most commonly involved are seabass or grouper, barracuda, snapper, parrotfish, wrasse, surgeonfish, and various other types of reef fishes.

The time of onset and symptomatology of ciguatera varies greatly according to the person, species of fish, toxicity, and amount and portion of fish ingested. Tingling about the lips, tongue, and throat followed by numbness may develop immediately or at any time within a period of 30 hours after the ingestion of the toxin. The usual time interval for the development of symptoms is from 1 to 6 hours. The initial symptoms in some instances consist of nausea, vomiting, metallic taste, dryness of the mouth, abdominal cramps, tenesmus, and diarrhea, followed by perioral tingling and numbness. The muscles of the mouth, cheeks, and jaws may become drawn and spastic with a feeling of numbness. Generalized symptoms of headache, anxiety, malaise, prostration, dizziness, pallor, cyanosis, insomnia, chilly sensations, fever, profuse sweating, rapid weak pulse, weight loss, myalgia, and joint aches are frequently present. Victims usually complain of a feeling of profound exhaustion and weakness. The feeling of weakness may become progressively worse until the patient is unable to walk. Muscle pains are generally described as a dull, heavy ache, or cramping sensation, but on occasion may be sharp, shooting, and affect particularly the arms and legs. Victims complain of their teeth feeling loose and painful in their sockets.

Visual disturbances, consisting of blurring, temporary blindness, photophobia, and scotoma, are common. Pupils are usually dilated and the reflexes diminished. Frequently reported are skin disorders, which are generally initiated by an intense generalized pruritus, followed by erythema, maculopapular eruptions, blisters, extensive areas of desquama-

tion—particularly of the hands and feet—and occasionally ulceration. There may also be a loss of hair and nails.

In severe intoxications, the neurotoxic components are especially pronounced. Paresthesias involve the extremities, and paradoxical sensory disturbances may be present in which the victim interprets cold as a "tingling, burning, dry-ice or electric-shock sensation," or hot objects may give a feeling of cold. In regard to the paradoxical sensory disturbance, the classical case usually cited is that in which an American naval officer who was poisoned by eating an amberjack was later observed subconsciously blowing on his ice cream, which was "burning" his tongue, in order to cool it. Ataxia and generalized motor incoordination become progressively worse. The reflexes are diminished and muscular paralyses develop. There may be clonic and tonic convulsions, muscular twitchings, tremors, dysphonia, dysphagia, coma, and death by respiratory paralysis. The limited morbidity statistics show a case fatality rate of about 7 percent. Death may occur within 10 minutes, but generally requires several days.

In those instances in which the victim survives, recovery is slow and convalescence may be very prolonged, with extreme weakness, sensory disturbances, and excessive weight loss being the last symptoms to disappear. When patients have survived severe intoxication, complete recovery has required a period of several years. Several workers have reported cases in which the symptoms persisted for as long as 25 years. Individuals who have been severely intoxicated have stated that during periods of stress, fatigue, exposure, or poor nutrition, there is a recurrence of the myalgia and joint aches similar to those suffered during the original acute period of the disease (*10*).

Gempylid Diarrhea

Some of the gempylids or escolars contain an oil within their flesh and bone marrow which has a pronounced purgative effect when ingested. Gempylid diarrhea (*27*) develops rapidly, and is said to be without cramping or pain. Since there are no other untoward effects, ingestion of the oil can hardly be considered as an intoxication in the usual sense of the word.

Treatment of Fish Poisoning

The treatment of fish poisoning is largely symptomatic. There are no specific antidotes, and an attack does not impart immunity. Gastric lavage and catharsis should be instituted at the earliest possible time. In many instances, 10 percent calcium gluconate given intravenously has given prompt relief, whereas in others it has been ineffective. Paraldehyde and ether inhalations have been reported to be useful in controlling the convulsions. Nikethamide or one of the other respiratory stimulants is advisable in cases of respiratory depression. In cases where excessive mucus production is a factor, aspiration and constant turning are essential. Atropine has been found to make the mucus more viscid and difficult to aspirate, and is not recommended. Oxygen by inhalation and intravenous administration of fluids supplemented with vitamins given parenterally are usually beneficial. If laryngeal spasm is present, intubation and tracheotomy may be necessary. In case of severe pain, opiates such as morphine, given in small divided doses, will probably be required. Cool showers have been found to be effective in relieving severe itching. Patients suffering from the paradoxical sensory disturbance should be given fluids slightly warm or at room temperature, as well as vitamin B complex supplements. Antihistaminic drugs will be found to be useful in the treatment of scombroid poisoning.

Prevention of Fish Poisoning

Scombroid fishes appear to be particularly susceptible to putrefaction and the development of toxic substances. Geiger has shown that the "histamine" content of the flesh of the Pacific mackerel, *Pneumatophorus diego*, increases from 0.9 mg. per 100 gm. of tissue to about 95 mg. per 100 gm. when kept at room temperature (20° to 25° C.) for about 10 hours (*28*, *33*). In warmer climates scombroids should be promptly refrigerated or eaten soon after capture. Toxic scombroid flesh cannot always be detected by appearance. The toxin

content may be very high with little or no evidence of putrefaction. Scombroid meat having a sharp or peppery taste should be discarded. If the whole fish is available the gills should be examined. Gills should be bright red and without evidence of off-odor. If there is the slightest evidence of putrefaction discard the fish.

If one eliminates scaleless fish from the diet there is no opportunity to come in contact with either tetraodontoids or moray eels, since both are without scales. In Japan, puffer fishes should be purchased from a first-class authorized restaurant having a licensed puffer cook. It is important that the individual preparing the food has a thorough knowledge regarding the fish and its toxicity. One can generally have this assurance by dealing only with the higher class restaurants. It is advisable to eliminate all of the visceral organs and skin from the diet regardless of the species. Although the testes are usually nontoxic, it must be kept in mind that this organ is frequently confused with the violently toxic ovaries, particularly during the season of the year in which the reproductive organs are in the dormant state.

Ordinary cooking does not inactivate the toxin. It may still be present in lethal quantities even when passed through a steam retort in the commercial canning process. The poison can be inactivated chemically by cooking the meat in a strong solution of sodium bicarbonate, ordinary baking soda, for a prolonged period of time. This latter technique also destroys the flavor of the fish and renders it useless for consumption.

Our knowledge regarding the toxicity of most species of tetraodontoid fishes, exclusive of Japanese forms, is exceedingly meager. We do know, however, that many of the tropical tetraodontoid species have produced violent death at one time or another. Unless a species is definitely known to be nontoxic, which is questionable even under the best of circumstances, all tropical forms should be eliminated from the diet.

If it is a question of survival—either eat the puffer or die—and the edibility of the fish is unknown, it is recommended that the fish be eviscerated promptly, and only the musculature be used. Moreover, the meat should be cut or torn into small bits, and soaked in water for a minimum of 3 or 4 hours. During this period the flesh should be kneaded while in the water, and the water changed at frequent intervals. The toxin is water-soluble and leaching will effectively remove it.

In dealing with potential ciguatera type of fishes it should be kept in mind that the most reliable methods of determining edibility involve the preparation of tissue extracts which are injected intraperitoneally into mice, or feeding samples of the viscera and flesh to cats, or dogs, and observing the animals for the development of toxic symptoms. Viscera, that is, liver and intestines of tropical marine fish should never be eaten. Also, the roe of most marine fish is potentially dangerous, and in some cases may produce rapid death. Fishes which are unusually large for their species should be discarded, particularly barracuda (*Sphyraena*), jacks (*Cranax*), and grouper (*Epinephelus*), during their reproductive season. If one is living under survival conditions and questionable fish must be eaten, it is advisable to cut the fish into thin fillets and soak them in several changes of water for at least 30 minutes. This will serve to leach out the poison which is readily water-soluble. Do not use the rinse water for cooking purposes. If a questionable species is cooked by boiling, the water should always be discarded. Again it should be pointed out that ordinary cooking procedures do not attenuate ichthyosarcotoxins.

Summary

Fish poisoning is a disease of antiquity. Fishes are believed to become poisonous as a result of their food habits—feeding on marine algae. There is no evidence that plankton or radioactive substances are a factor in the production of the poisons. Poisonous fishes are largely circumtropical in their distribution. Toxin content is greatest in puffers during their reproductive season of the year, but this is probably not true of most other fishes. The distribution of the toxin within the body of the fish is subject to considerable fluctuation, but if the fish is poisonous, some of the poison will be present in the viscera in about 90 percent of the cases. Poisonous fishes cannot be detected by their appearance.

Fish poisoning should not be confused with bacterial food poisoning, with which it has no etiological connections. The overall incidence of fish poisoning is not known. There are eight clinical types of ichthyosarcotoxism recognized at present. With the exceptions of gempylid diarrhea and scombroid poisoning, all other types of ichthyosarcotoxism are characterized by neurotoxic symptoms. The treatment of fish poisoning is symptomatic. Little is known about the chemical and pharmacological properties of fish poisons.

REFERENCES

(*1*) Gaillard, C.: Recherches sur les poissons représentés dans quelques tombeaux égyptiens de l'ancien empire. Mém. Inst. Français Arch. Orient. 51: 97–100 (1923).

(*2*) Autenreith, H. F.: Ueber das Gift der Fische. Tübingen, C. F. Osiander, 1833, 287 pp.

(*3*) Gudger, E. W.: Poisonous fishes and fish poisoning, with special reference to ciguatera in the West Indies. Am. J. Trop. Med. 10: 43–55, January 1930.

(*4*) Baughman, J. L.: The marine fisheries of the Mayas as given in Diego de Landa's "Relacion de las cosas de Yucatan" with notes on the probable identification of fishes. Texas J. Sc. 4: 432–459, April 1952.

(*5*) Phisalix, M.: Animaux venimeux et venins. Paris, Masson et Cie., 1922, vol. 1, pp. 487–628.

(*6*) Gilman, R. L.: A review of fish poisoning in the Puerto Rico-Virgin Islands area. U. S. Nav. Med. Bull. 40: 19–27, January 1942.

(*7*) Hiyama, Y.: Report on the research on poisonous fishes of the South Seas. Odawara, Japan, Nissan Fisheries Experiment Station, 1943, pp. 1–137. Also English translation *in* U. S. Fish and Wildlife Service Spec. Scient. Rep. No. 25. Washington, D. C., U. S. Government Printing Office, 1950, pp. 1–188.

(*8*) Arcisz, W.: Ciguatera, tropical fish poisoning. U. S. Fish and Wildlife Service Spec. Scient. Rep. No. 27. Washington, D. C., U. S. Government Printing Office, 1950, pp. 1–23.

(*9*) Fish, C. J., and Cobb, M. C.: Noxious marine animals of the central and western Pacific Ocean. U. S. Fish and Wildlife Service Res. Rep. No. 36. Washington, D. C., U. S. Government Printing Office, 1954, pp. 1–45.

(*10*) Halstead, B. W., and Lively, W. M.: Poisonous fishes and ichthyosarcotoxism. U. S. Armed Forces M. J. 5: 157–175, February 1954.

(*11*) Whitley, G. P., and Halstead, B. W.: An annotated bibliography of the poisonous and venomous fishes of Australia. Rec. Australian Mus. 23: 211–227, September 1955.

(*12*) Ross, S. G.: Preliminary report on fish poisoning at Fanning Island (Central Pacific). M. J. Australia 2: 617–621, Nov. 22, 1947.

(*13*) Halstead, B. W.: Current status of research on Pacific poisonous fishes and ichthyosarcotoxism. *In* Symposium on venoms, edited by E. B. Buckley and Nandor Porges. American Association for the Advancement of Science Pub. No. 44. Washington, D. C., 1956, pp. 29–32.

(*14*) Kawabata, T., Halstead, B. W., and Judefind, T. F.: A report of a series of recent outbreaks of unusual cephalopod and fish intoxications in Japan. Am. J. Trop. Med. & Hyg. 6: 935–939 (1957).

(*15*) Halstead, B. W.: Ichthyotoxism. A neglected medical problem. M. Arts & Sc. 5: 115–121, Fourth Quarter, 1951.

(*16*) Halstead, B. W., and Bunker, N. C.: A survey of the poisonous fishes of the Phoenix Islands. Copeia 1954: 1–11, January.

(*17*) Dawson, E. Y., Aleem, A. A., and Halstead, B. W.: Marine algae from Palmyra Island with special reference to the feeding habits and toxicology of reef fishes. Allan Hancock Found. Pub. Occ. Pap. 17: 1–39 (1955).

(*18*) Habekost, R. C., Fraser, I. M., and Halstead, B. W.: Observations on toxic marine algae. J. Washington Acad. Sc. 45: 101–103, April 1955.

(*19*) Fukuda, T., and Tani, I.: Statische Beobachtung über die Fuguvergiftung. Japanese J. M. Sc. (IV. Pharm.) 10: 48–50 (1937).

(*20*) Fukuda, T.: Violent increase of cases of puffer poisoning. Rinsho to Kenkyu 29: 5–12, February 1952.

(*21*) Steinbach, E.: Bericht über die Gesundheitverhältnisse der Enigeborenen der Marshall-Inseln im Jahre 1893–94 und Bemerkung über Fischgift. Mitt. Forschung. Gelehrt. Deutsch. Schutzgeb. 8: 157–171 (1895).

(*22*) Matsuo, R.: Study of the poisonous fishes at Jaluit Island. Nanyo Gunto Chihobyo Chosa Ronbunshu 2: 309–326 (1934).

(*23*) Yasukawa, T.: Report of an investigation of poisonous fishes within the jurisdiction of the Saipan branch of the Government-General. Tokyo, Imperial University Contagious Disease Research Institute, 1935. Also English translation *in* U. S. Fish and Wildlife Service Spec. Scient. Rep. No. 25. Washington, D. C., U. S. Government Printing Office, 1950, pp. 189–197.

(*24*) Halstead, B. W.: Some general considerations of the problem of poisonous fishes and ichthyosarcotoxism. Copeia 1953: 31–33, January.

(*25*) Khlentzos, C. T.: Seventeen cases of poisoning due to ingestion of an eel, *Gymnothorax flavimarginatus*. Am. J. Trop. Med. 30: 785–793 (1950).

(*26*) Ralls, R. J., and Halstead, B. W.: Moray eel poisoning and a preliminary report on the action of the toxin. Am. J. Trop. Med. & Hyg. 4: 136–140, January 1955.

(27) Gudger, E. W.: A new purgative, the oil of the "castor oil fish," *Ruvettus*. Boston M. & Surg. J. 192: 107–111, March 1925.

(28) Geiger, E.: Histamine content of unprocessed and canned fish. A tentative method of quantitative determination of spoilage. Food Res. 9: 293–297 (1944).

(29) Halstead, B. W., and Schall, M. C.: A report on the poisonous fishes captured during the Woodrow G. Krieger expedition to the Galapagos Islands. *In* Essays in the natural sciences in honor of Captain Allan Hancock. Los Angeles, University of Southern California Press, 1955, pp. 147–172.

(30) Halstead, B. W., and Schall, M. C.: A report on the poisonous fishes captured during the Woodrow G. Krieger expedition to Cocos Island. Pacific Sc. 10: 103–109, January 1956.

(31) Courville, D. A., Halstead, B. W., and Hessel, D. W.: A review of the literature concerning the chemistry of marine biotoxins. Chem. Rev. In press.

(32) Engelsen, H.: Om giftfisk og giftige fisk. Nord. hyg. tidskr. 3: 316–325 (1922).

(33) Kawabata, T., Ishizaka, K., and Miura, T.: Studies on the food poisoning associated with putrefaction of marine products. III. Physiological and pharmacological properties of newly isolated vagus-stimulant, named "saurine" (in Japanese). Bull. Japanese Soc. Scient. Fish. 21: 347–351 (1955).

"Model" Law to Cut Poison Deaths

The American Medical Association's Committee on Toxicology has formulated a "model" law for the precautionary labeling of hazardous substances in commercial, household, and industrial chemical products.

The labeling would apply to hazardous substances defined as toxic, irritating, sensitizing, corrosive, flammable, explosive, or radioactive under customary or reasonably anticipated conditions of handling or use.

"Model" text would require declaration of hazardous ingredients and warning statements on the label and in the literature accompanying chemical products.

Requirements of the model law are:

• Labeling of all chemical products containing hazardous substances that are not now regulated.

• Applications of the same labeling standards to chemicals for domestic use and for export. (This will refute the common complaint that inferior standards apply to foreign customers.)

• Prohibition of re-use of food and drug containers bearing their original labels.

• Identification and warnings for strongly sensitizing chemicals which cause allergic or inflammatory reactions in living tissue on contact.

A significant departure in the new law is the deletion of the word "poison." Reference standards, based on animal tests, provide a more consistent and reliable index of poisonous properties than did the former label, according to the committee, not only because there are variations in existing legal limits for poison but also because there is a lack of agreement among scientists on a definition of the term.

Inadequate labeling of potentially harmful chemicals, the committee reports, has been a major handicap to a successful attack on the problem of accidental poisoning. Moreover, lack of information about hazardous ingredients may complicate or delay treatment in emergency situations.

The committee's work in formulating a model law was endorsed by various organizations such as the National Drug Trade Conference, the American Public Health Association, the Cincinnati Academy of Medicine, and the Pennsylvania Pharmaceutical Association.

Heart Disease

Following are two of the papers presented at a session devoted to heart disease during the September 1957 meeting of the American Statistical Association in Atlantic City, N. J.

Methods of Studying the Ecology of Coronary Heart Disease

MORTON ROBINS, M.S.P.H., and
ALFRED M. STEINMAN, M.D.

DURING the past 2 years we have witnessed a tremendous surge of interest in the ecology of coronary heart disease. A conference on the epidemiology of atherosclerosis and hypertension (*1*), a symposium on measuring the risk of coronary heart disease (*2*), and numerous papers and articles on this leading cause of death (*3–5*)—all have served to whet the appetite of both the medical and public health profession for more definitive data. The public is looking for widespread programs for control or prevention, but while our knowledge of coronary heart disease has increased and many leads on etiological factors have been obtained, preventive programs have not yet been recommended. Emphasis is still on the need for additional research into causation.

The development of coronary heart disease is generally agreed to be the result of complex, unidentified interactions between the human host, with his variable susceptibility, either genetic or acquired, and his total environment.

The study of such interactions is called "human medical ecology" (*6*) or "scientific epidemiology" (*7, 8*). Ecology emphasizes the nature of multiple causation and seeks to integrate the diversity of factors involved in disease and to synthesize hypotheses on causation. The ecologic approach has rarely been used in epidemiological investigations of infectious diseases since these studies have been concerned principally with identification of the causative agent—the micro-organism. Interest in medical ecology was revived when epidemiological inquiry was broadened to encompass the noninfectious chronic diseases of unknown etiology. Thus, medical ecology and epidemiology are blood brothers.

The ecologic approach is new, complicated, and expensive. Because of the shortages of trained investigators—at times requiring a team composed of clinician, epidemiologist, biostatistician, and experts from the basic and applied sciences—only a small number of epidemiological studies are currently under way. There is therefore a need to examine our resources and choose our studies with circumspection.

Considering the variation in age-specific incidence rates, the difficulty of accurate diagnosis, and the chronic nature of the disease, which of the alternative methods of data collection is best

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suited to study causation? An evaluation of the various data collection methods may give some perspective in making a proper choice. A review of ecologic factors may also reveal opportunities for field studies.

Ecologic Factors

Coronary heart disease is ubiquitous, with increasing morbidity and mortality in both young and old. Physicians are able, to some extent, to treat the result of the disease, but they are unable to prevent it. Prevention must hinge upon a better understanding of the basic role that each of the many known, suspected, and as yet unknown factors play in the creation of a thrombus in a coronary artery which has become atherosclerotic.

Factors incriminated as causes of the disease have been identified or evaluated in monographs and texts on coronary heart disease (*9*, *10*). An excellent summarization of our current state of knowledge concerning the pathogenesis of the disease is found in a recent paper by Miller and associates (*4*), and in the report of the Conference on Epidemiology of Atherosclerosis and Hypertension (*1*). In order to serve as a backdrop for the discussion of study methods, a brief description follows of what we believe to be the factors which require special investigation.

Experimental studies designed to produce atherosclerosis deliberately in animals have led to implications currently being utilized in planning clinical studies in humans, for example, hormone and diet studies. However, the experimental lesions produced in animals are rarely associated with thrombosis, which leads to the suspicion that blood coagulability may be altered.

Another approach to identification of etiological factors is through correlative, fact-finding studies. In essence, most of these studies seek to establish the association of a given physical feature, habit pattern, or result of a physiological or chemical test with the presence of the disease.

The clinician is aware of certain seemingly hereditary factors which appear to be of some importance. Coronary heart disease is observed more frequently in mesomorphs than in other somatotypes (*11*). In many instances, the disease is seen in each generation of a given family (*12*). This suggests the probability that certain basic differences—anatomical, psychological, metabolic, or mechanical—exist among members of such families as compared with other groups. This feeling is strengthened by the observation that a synergistic relationship exists between coronary heart disease and certain other diseases with familial concentrations, that is, diabetes, xanthomatosis, hypercholesterolemia, and hypertension (*13*, *14*). These conditions are considered significant when present in males under age 40, and perhaps even more so, in females.

Since some people are nearly entirely free of atheromata while others have dramatic depositions, some basic metabolic defect must be suspected which produces the atheromatous substances. Atherosclerotic plaques may be formed not only in the coronary arteries but in the vessels of the brain, legs, and other body organs and sites. A further question arises from the lack of uniformity in the distribution of atherosclerosis—the presence of plaques at one site bears no necessary relationship to their presence or absence at other principal locations. In addition, in hens, estrogens inhibit the incidence of experimental coronary but not aortic atherosclerosis (*15*).

Other factors, categorized as environmental influences, also play a role. The effect of climatic changes, ultraviolet light, and smoking have been incriminated. Nutrition probably has an important relationship to the metabolic dysfunction possibly involved in the pathogenesis of the disease. However, specific dietary factors have not as yet been "validated." The relative role of physical activity and the reactions to mental, physical, and biological stress are other significant variables that need further study and quantification.

In regard to the direction of concentrated research in the future, the group of patients under age 40 with an accelerated form of the disease may provide the best source of information ecologically. How do those with manifestations of the disease differ from others in their genetic makeup and habit patterns, including

diet, occupation, mode of living, and associated disease? If significant differences are discovered, are they coexistent or correlated?

The answer to these and many other questions will lead to newer ones. These in turn will lead to the attack upon what we believe is the underlying process: a metabolic defect which produces either atherosclerotic or thrombotic changes, or both, in the coronary arteries, accelerated by such factors as diet, hormonal changes, and habit patterns.

Epidemiological Approaches

Let us now consider the epidemiological approaches in the search for causes of coronary heart disease. We can classify these methodologies into six broad categories: mortality data, hospital statistics, morbidity surveys, morbidity reporting, longitudinal studies, and selected patient cohorts.

Mortality Data

Information on death certificates has traditionally been analyzed to supply clues on statistical associations between demographic characteristics of the population and the incidence of disease. Inferences from analyses of mortality figures have often been substantiated by findings from other epidemiological studies. A large number of statistical studies of coronary heart disease mortality data have been made, and significant differences have been reported for such factors as age, sex, marital status, income, occupation, ethnic group, height, and weight (*1*). The relationship between dietary fat consumption and coronary heart disease mortality reported by Keys has recently been challenged by Yerushalmy and Hilleboe (*16*).

It has been suggested that mortality analyses should be pursued because the source data are readily accessible and the study costs are low compared with other epidemiology approaches (*1*). Moreover, more intensive studies can be designed to increase the epidemiological significance of observed mortality differentials. These mortality studies would start with facts on death certificates and then add information by means of field investigations or by questionnaires to the attending physician and relatives of the decedent. In addition to gathering facts on events leading to death, the studies might provide valuable information on the accuracy of cause of death certification. More profitable coronary heart disease mortality data can also be derived from studies in selected localities where death certification practices are believed to be fairly uniform and accurate.

The major weaknesses of mortality statistics on coronary heart disease as a source of ecologic data are: first, variation in the completeness and accuracy in medical certification of deaths due to the disease; second, questionable correlation between specific mortality rates and incidence of the disease; and third, the impossibility of analyzing from routine tabulations of mortality data many of the ecologic factors believed to be significant in the pathogenesis of the disease.

Accuracy and completeness of cause of death certification depend on the quantity and quality of available physicians' services, and vary with concepts held by physicians concerning the

Guide for Avoiding Arteriosclerosis

A statement advising laymen on how to resist arteriosclerosis, coronary thrombosis, and brain thrombosis has been issued by the National Health Education Committee, Inc., of New York City.

According to the physicians who signed the statement, Dr. Paul D. White, Dr. Howard B. Sprague, Dr. Samuel A. Levine, and Dr. Frederick J. Stare, all of Boston, there are five predisposing factors. They are listed as heredity, overweight, elevated cholesterol level, elevated blood pressure, and excessive cigarette smoking. Hard work in itself, they maintained, cannot be considered a factor.

Persons with a strong hereditary background of arteriosclerosis are particularly cautioned to minimize the effects of the other factors.

The statement lists a number of documents referring to the factors listed. Stressing the importance of arteriosclerosis of the heart and brain, the statement noted that heart and circulatory disease caused the largest number of deaths in the United States. Of the 843,410 deaths in 1956 in this category, most were due to arteriosclerosis.

manifestations of coronary heart disease. These differences in death reporting practices in various subgroups of the population can alter the actual association of coronary heart disease mortality and a particular demographic characteristic (*17*). Yerushalmy and Hilleboe's study of heart disease mortality statistics for different countries indicates that large numbers of coronary heart disease deaths are reported variably, and are classified as "degenerative heart disease" or as "other diseases of heart" (*16*).

A basic epidemiological question is whether differential mortality can be used as an index of the relative incidence of initial coronary heart disease attacks among specific population groups, since the disease is chronic and most initial attacks are not fatal. Attacks often recur over a period of many years before the fatal attack occurs. Thus, the age distribution of deaths from the disease may be markedly different from that of patients having an initial attack. Moreover, survivors of an initial attack frequently change their occupation to compensate for their residual disability or from fear of physical exertion. These facts should be recognized in evaluating the epidemiological significance of the mortality differentials of the disease by age, income, occupation, socioeconomic status, and place of residence.

Notwithstanding their limitations, mortality data provide an index of the size and seriousness of the problem. In the absence of specific morbidity and case fatality data, analyses of mortality trends supply indirect evidence of changes in incidence or advances in therapeutic procedures.

Hospital Statistics

The growth of hospital facilities accompanying the expansion of hospitalization insurance coverage and medical care for indigents suggests the increased usefulness of hospital statistics as a measure of coronary heart disease morbidity. Some merit is attached to proposals for a statistical study of coronary heart disease admissions or discharges from a group of hospitals that supply all the inpatient care requirements of a particular area. An example of integrated hospital statistics for a known population is provided by the experience of the Saskatchewan Hospital Services Plan (*18*). In the United States, the Commission on Professional and Hospital Activities, Inc. (Ann Arbor), has assembled detailed statistics on patients discharged since January 1, 1953, from hospitals comprising the Southwestern Michigan Hospital Council.

Hospital statistics are considered by some to represent, at worst, a compromise between mortality statistics and complete morbidity data. Extensive hospital morbidity surveys were conducted in New York City in 1933 (*19*), in Oxford, England, in 1943 (*20*), and in Ontario, Canada, in 1951 (*21*). More recently, a large pilot study was conducted in New York City to demonstrate the feasibility of a hospital reporting system as a source of providing useful information on morbidity and for planning medical care programs (*22*).

While the data on coronary heart disease in tabulations of hospital records suggest differentials in morbidity, their validity has not been ascertained. The question still unanswered is whether the differentials in hospital admission rates are comparable to those based on total incidence of coronary heart disease according to sex, age, race, occupation, and other demographic characteristics. Studies are needed to correlate hospital statistics for a community with estimates of morbidity. In such studies analysis should be made separately for each of the manifestations of coronary heart disease, that is angina pectoris, abnormal electrocardiogram not related to other disease states, and myocardial infarction. Until these questions are answered, indexes of morbidity from hospital admission rates require confirmation by other epidemiological studies.

Detailed clinical, laboratory, and medical history data on hospitalized coronary heart disease patients may also supply leads for other statistical associations related to ecologic factors.

Morbidity Surveys

Morbidity surveys on the health status of a population may take two forms: interviews in sample households, or a complete canvass of physicians and hospitals in a community.

To our knowledge, such a complete survey of physicians and hospitals has not been applied

to the study of coronary heart disease morbidity, but it has been used to obtain morbidity data on cancer. The canvass method is expensive and requires protracted negotiations with medical societies, hospital associations, and health departments. Although the method has been practicable occasionally for cancer morbidity surveys, its results would be highly questionable when applied to coronary heart disease. As contrasted with cancer where pathological laboratory records, hospital records, and mortality reports form a large part of the total morbidity picture, the canvass method applied to coronary heart disease morbidity would rely primarily on reports by cooperating physicians. Retrospective reporting of coronary heart disease is not, therefore, likely to yield a complete picture of its incidence during a prior year.

Morbidity surveys using data from household interviews of a scientifically selected sample of a community, a State, or the Nation have provided epidemiological data on coronary heart disease. An appraisal of heart disease morbidity derived from the National Health Survey of 1935–36 was made by Collins (*23*) in 1949. More recently, findings have been reported based on morbidity surveys conducted in Hunterdon County, N. J. (*24*), Baltimore, Md. (*25*), and the State of California (*26*). All of these reports generally agree on the uncertain validity of the computed prevalence rates for such chronic diseases as coronary heart disease. Incidence rates derived from data obtained in household surveys are even more tenuous.

Comparisons of coronary heart disease prevalence as measured by household interviews and clinical examinations indicate that the interview data provide minimum estimates. It would also appear that the reported prevalence rates for various subgroups of the surveyed population are subject to varying correction factors of uncertain magnitude.

Despite these limitations, valuable demographic and epidemiological data are byproducts of household morbidity surveys. Estimates are obtained of ecologic characteristics not otherwise available. Such data are useful in assessing concurrent data from morbidity reporting projects, and hospital and mortality studies of the same community. The survey may also supply rosters of individuals presumably free of coronary heart disease. These randomly selected persons can serve as controls for study patients identified by other study methods.

Morbidity Reporting

Ideally, voluntary reporting by physicians of all new cases of coronary heart disease as they are diagnosed provides the cheapest and most direct approach for acquiring data on incidence. In an appeal in 1930 for voluntary reporting by New York State physicians of certain facts relating to heart disease, Dr. J. V. DePorte, of the New York State Department of Health, said, "In this day, when the immutability of even chemical elements is no longer an axiom, the rigid grouping of diseases into communicable and noncommunicable seems to be altogether artificial. . . . A group of diseases which incapacitate about 300,000 persons in the State is certainly a matter that cannot be excluded from the field of legitimate public health activities by the mere fiat of our individualistic tradition (*27*)." No action was ever taken on his proposal.

In 1956, Dr. P. D. White called attention to the increased collaboration between the epidemiologist, the cardiologist, and the family doctor as illustrated by their participation in an epidemiological survey of coronary heart disease in the Grand Forks, N. Dak., area (*28*). During this survey all physicians in the area notified a central committee of each new case of coronary heart disease diagnosed. The reports were supplemented by a household survey giving descriptive data of the population in terms of ethnic background, diet, exercise, habits, stress, smoking habits, and other characteristics. Rosters of the surveyed group are matched against cases of coronary heart disease reported and act as controls in followup studies of both groups. A similarly organized study started in January 1956 in Middlesex County, Conn.

Despite this and other evidence of increased community and physician interest in coronary heart disease, it does not appear likely that voluntary reporting is a practical approach in many localities.

More realistic perhaps is the use of this ap-

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proach to determine the incidence of coronary heart disease among more circumscribed groups. Valuable ecologic data can be assembled, for example, on persons covered by comprehensive medical care programs where both physician services and medical records are integrated.

Longitudinal Studies

In prospective or followup studies of coronary heart disease, a cohort of the general population, considered to be free of the disease, is observed over a long period of time to determine the natural history of the disease process. Information is sought on signs or symptoms considered to be precursors to clinical manifestations of the disease. The incidence of conditions can be related to multiple characteristics of the study population which are ascertained by interview, medical examination, or diagnostic tests. Prognosis can be measured in terms of progression of clinical signs and symptoms with reference to the characteristics of each case. In a longitudinal study, provision can also be made after the study has started to introduce a new study variable meriting investigation.

The major limitations of longitudinal studies are: (*a*) technical difficulties in organizing the study and high costs over the long period required for data collection; (*b*) attrition of the study group due to noncooperation or movement out of the study area; (*c*) change of observers throughout the course of the study; and (*d*) changes in the normal living patterns of the study subjects when they are conscious of the existence of precursors to clinical coronary heart disease.

The first two limitations lead to the question of how to select the study population. Should the study group be a sample of the general population? Or should the study group include all or a sample of a specially constituted group? Obviously, study of the general population permits more valid generalization. However, studies of specially constituted groups, such as industrial employees, Veterans Administration beneficiaries, and participants of pension, disability, or health insurance plans, have the advantages of lower attrition rates and greater cooperation of the study group. Moreover, study costs are appreciably lower, since medical and laboratory facilities are available and medical records are generally maintained for other medical care purposes.

While selection factors may be present with such variables as age, sex, race, activity status, and income, the observed experience of selected groups can be adjusted by available biometric techniques. In this connection, approximately the same average annual incidence of coronary heart disease, 7 per 1,000, was observed among male civil service employees in the age group 40–54 in Albany, N. Y. (*29*), and in Los Angeles, Calif. (*30*), as was found in a sample of the total male residents of Framingham, Mass. (*31*), in the same age group.

Selected Patient Cohorts

Coronary heart disease patients, or persons having a disease believed to be synergistic in the pathogenesis of heart disease, provide special cohorts for ecologic study. Ideally, these study groups should be scientifically selected from the general universe of patients with the disease. Practical considerations, however, commonly lead to a decision to select hospitalized patients or outpatients as a study unit.

How representative such a group is of the general class of patients from which it is drawn and the methodology of the study plan are concerns of the statistician. The restrictions on the interpretation of findings and the procedures necessary to avoid either erroneous or spurious statistical associations have already been described by Berkson (*32*), Kraus (*33*), Lilienfeld (*34*), and Moore (*35*). With proper concern for the study design, patient cohorts furnish excellent case material for the study of metabolic defects and specific environmental influences as they relate to the incidence of coronary heart disease.

Retrospective study of coronary heart disease cases generally consists of inquiry into their medical history for suspected antecedent events. Comparison with similar data from a control population provides an indirect method for estimating differential incidence rates. However, when hospitalized patients are used as the study group, the validity of procedures for estimating relative risks (*36*) is dependent on the degree to which the hospital patients

and the selected controls are representative of these same groups in the general population.

Generally speaking, the longitudinal rather than the indirect approach is recommended for the study of diseases with relatively high incidence. While the total incidence of coronary heart disease is considered to be sufficiently high for longitudinal studies, the incidence among adults under 40 years of age has been found to be so low that the use of the retrospective approach is suggested for this age group. The study of coronary heart disease among these young adults, particularly those without evidence of hypercholesterolemia, hypertension, or diabetes, is of special ecologic interest. This group of patients represents an accelerated form of atherosclerosis.

"Recovered" coronary heart disease patients also serve as cohorts for prospective studies to evaluate the effectiveness of control or prophylactic measures in preventing recurrent attacks. These exploratory studies may provide an understanding of at least one of the components of the causative complex. The advantages of using a cohort of patients instead of a sample of the general population are fairly obvious.

Prospective, longitudinal studies of individuals considered to be particularly susceptible to coronary heart disease, such as diabetics and hypertensives, should also be pursued more intensively than in the past. The size of such cohorts need not be as large as those for longitudinal studies of the general population since the expected differential incidence rates are higher. Moreover, longitudinal studies of these patient groups may possibly suffer from less attrition because of greater interest in their disease. Determination of the environmental factors which trigger symptomatology among these highly susceptible individuals would add significantly to our understanding of the ecology of the disease.

Summary

Public health authorities, who are confronted with the task of reducing the incidence of coronary heart disease, must base their policies and programs on knowledge of the causes. A review of ecologic factors indicates that future preventive programs will probably be related to the control of the causes of coronary atheroma and of the environmental influences which accelerate atheromatous depositions and coronary thrombosis.

Epidemiological data are needed to define the differential incidence of the disease among persons with different characteristics and living under different environmental conditions. Such data, when added to pertinent knowledge derived from clinical sources, animal experimentation, and laboratory sciences, will eventually enable the medical ecologist to synthesize a pattern of the multiple causative factors involved.

From this review it is evident that no one all-encompassing field study is likely to settle the epidemiology of coronary heart disease. Significant evidence on causation can be derived from one approach which is not within the capabilities of another. However, because of the short supply of technicians needed for epidemiological research, it is necessary to proceed piecemeal in order to fill the important gaps in our knowledge.

Hypotheses should be intensively investigated by the most rigorous epidemiological method available, despite known limitations in our ability to generalize from the findings. This recommendation does not imply indiscriminate collection of information nor disregard for the principles of validity and reliability.

Three approaches are suggested for future epidemiological studies of coronary heart disease:

1. Routine reporting for a limited time period of initial manifestations of coronary heart disease among adult populations whenever practicable.

2. Longitudinal studies of selected groups whose physical, physiological, and psychological characteristics are determined at the beginning of the observation period.

3. Retrospective and prospective studies of patient populations to determine the relationship between underlying metabolic defects and environmental influences and the incidence of coronary heart disease.

REFERENCES

(*1*) American Heart Association: Conference on Epidemiology of Atherosclerosis and Hyper-

tension, held at Arden House, Harriman, N. Y., January 29–February 2, 1956. New York, N. Y., 1956, 88 pp.

(2) Measuring the risk of coronary heart disease in adult population groups. A symposium. Am. J. Pub. Health (supp.) 47: 1–63, April 1957.

(3) Enterline, P. E., and Stewart, W. H.: Geographic patterns in deaths from coronary heart disease. Pub. Health Rep. 71: 849–855, September 1956.

(4) Miller, D. C., Stare, F. J., White, P. D., Gordon, J. E., and Ingalls, T. H.: The community problem in coronary heart disease: A challenge for epidemiological research. Am. J. M. Sc. 232: 329–359, September 1956.

(5) Keys, A.: Calories and cholesterol. Geriatrics 12: 301–310, May 1957.

(6) James, G., and Greenberg, M.: The medical officer's bookshelf on epidemiology and evaluation. Part I. Epidemiology. Am. J. Pub. Health 47: 401–408, April 1957.

(7) Dudley, S. F.: Ecological outlook on epidemiology. Proc. Roy. Soc. Med. 30: 57–70, November 1936.

(8) Gregg, A.: The future health officer's responsibility: Past, present, and future. Am. J. Pub. Health 46: 1384–1389, November 1956.

(9) Plotz, M.: Coronary heart disease. New York, N. Y., Hoeber-Harper, 1957, 353 pp.

(10) White, P. D.: Heart disease. Ed. 4. New York, N. Y., Macmillan, 1951, 1,015 pp.

(11) Spain, D. M., Bradese, V. A., and Huss, G.: Observations on atherosclerosis of coronary arteries in males under age 46: Necropsy study with special reference to somatotypes. Ann. Int. Med. 38: 254–277, February 1953.

(12) Gertler, M. M., and White, P. D.: Coronary heart disease in young adults. Cambridge, Mass., Harvard University Press, 1954, 218 pp.

(13) Lober, P. H.: Pathogenesis of coronary sclerosis. Arch. Path. 55: 357–383, May 1953.

(14) Thomas, C. B., and Cohen, B. H.: The familial occurrence of hypertension and coronary artery disease, with observations concerning obesity and diabetes. Ann. Int. Med. 42: 90–127, January 1955.

(15) Stamler, J., Pick, R., and Katz, L. N.: Inhibition of cholesterol-induced coronary atherogenesis in egg-producing hen. Circulation 10: 251–254, August 1954.

(16) Yerushalmy, J., and Hilleboe, H. E.: Fat in the diet and mortality from heart disease. New York State J. Med. 57: 2343–2354, July 15, 1957.

(17) Lew, E. A.: Variations in mortality from coronary disease. Statist. Bull., Metrop. Life Insur. Co. 38: 1–3, June 1957.

(18) Saskatchewan Department of Public Health: Annual report of the Saskatchewan Hospital Services Plan, 1956. Regina, 1957.

(19) Deardorf, N. R., and Fraenkel, M.: Hospital discharge study. New York, N. Y., New York City Welfare Council, 1942–1943, 3 vols.

(20) Cotton, H.: Medical records; Their purposes and uses. Hospital (London) 44: 57–61, February 1948.

(21) Davis, G. D.: Hospital morbidity study. Report to the Minister of Health for Ontario. Toronto, 1954.

(22) Fraenkel, M., and Erhardt, C. L.: Morbidity in the municipal hospitals of the City of New York. New York, N. Y., Russell Sage Foundation, 1955, 229 pp.

(23) Collins, S. D.: Statistical studies of heart disease; Illness from heart and other cardiovascular-renal diseases recorded in general morbidity surveys of families. Pub. Health Rep. 64: 1439–1492, Nov. 18, 1949.

(24) Trussell, R. E., Elinson, J., and Levin, M. L.: Comparisons of various methods of estimating the prevalence of chronic disease in a community—The Hunterdon County study. Am. J. Pub. Health 46: 173–182, February 1956.

(25) Krueger, D. E.: Measurement of prevalence of chronic disease by household interviews and clinical evaluations. Am. J. Pub. Health 47: 953–960, August 1957.

(26) Drake, R. M., Buechley, R. W., and Breslow, L.: An epidemiological investigation of coronary heart disease in the California health survey population. Am. J. Pub. Health (supp.) 47: 43–57, April 1957.

(27) DePorte, J. V.: Heart disease in the State of New York. A statistical review of mortality and morbidity. Am. Heart J. 5: 652–659, June 1930.

(28) White, P. D.: The cardiologist enlists the epidemiologist. Am. J. Pub. Health (supp.) 47: 1–3, April 1957.

(29) Doyle, J. T., Heslin, A. S., Hilleboe, H. E., Formal, P. F., and Korns, R. F.: A prospective study of degenerative cardiovascular disease in Albany: Report of three years' experience. I. Ischemic heart disease. Am. J. Pub. Health (supp.) 47: 25–32, April 1957.

(30) Chapman, J. M., Goarke, L. S., Dixon, W., Loveland, D. E., and Phillips, E.: The clinical status of a population group in Los Angeles under observation for two to three years. Am. J. Pub. Health (supp.) 47: 33–42, April 1957.

(31) Dawber, T. R., Moore, F. E., and Mann, G. V.: Coronary heart disease in the Framingham study. Am. J. Pub. Health (supp.) 47: 4–24, April 1957.

(32) Berkson, J.: Limitations of the application of fourfold table analysis to hospital data. Biometrics Bull. 2: 47–53, June 1946.

(33) Kraus, A. S.: Use of hospital data in studying association between characteristic and disease. Pub. Health Rep. 69: 1211–1214, December 1954.

(34) Lilienfeld, A. M.: Epidemiological methods and inferences in studies of noninfectious diseases. Pub. Health Rep. 72: 51–60, January 1957.
(35) Moore, F. E.: Problems in selection of universe for study of chronic illness. Milbank Mem. Fund Quart. 31: 242–246, July 1953.
(36) Cornfield, J.: Method of estimating comparative rates from clinical data. Applications to cancer of lung, breast, and cervix. J. Nat. Cancer Inst. 11: 1269–1275, June 1951.

Some Observations on the Epidemiology of Heart Disease

TAVIA GORDON

CERTAINLY, the problems in studying heart disease are complex and difficult. To discuss them in detail is obviously impossible here. I will therefore confine myself to a few simple observations.

The first is that the study of heart disease is to a considerable degree still a study of deaths. All too often the first indication we have that a person's coronary artery isn't all it ought to be is when he dies. The final evaluation of an attack of coronary artery disease requires an analysis of changes in the coronary artery and this can be done only by autopsy. There is no equivalent to the biopsy in the study of heart disease.

The second observation is that we must make a distinction between the age group under 65 and the age group over 65 years. When we speak of the alarming increase in heart disease in this country we are referring to the rise in mortality among white men aged 45–64. When we speak of the difficulties of diagnosis we are referring primarily to events after age 65 and secondarily to events among middle-aged women, which are apt to be equivocal.

The study of heart disease among old people is really for the future. I doubt whether medical science is far enough advanced at present to adequately describe the complexity of chronic illness at advanced ages. Medical pathology is certainly of little help. Usually, the pathologist's report clearly indicates that the person was extensively diseased; the wonder is that he lived as long as he did; but it is difficult to delimit from the multiplicity of defects present any specific, well-defined etiology. Nor is the clinical picture much more help. As has been pointed out, all the organ systems fail at death—the lungs, the liver, the kidneys, and so forth, as well as the heart—but in the absence of a clear-cut etiology the failure of the heart will tend to dominate the picture. If, however, we confine our attention to the study of coronary artery disease among middle-aged men I think we are in a good position to tag our cases and to investigate the epidemiology of the disease.

Unfortunately, vital statistics has gotten itself into a dilemma in the reporting of deaths among older people. If a doctor, faced with a complex and poorly defined pathology, reports a death as due to "old age," the local registrar will in all likelihood request a more definite cause of death. Any student of medical ecology knows what happens next. After a while the doctor starts giving definite answers even when he has only the vaguest notion of the cause of death. And then, of course, the vital statistician becomes understandably skeptical about the reporting of cause of death.

This skepticism about the reporting of cause of death, which is practically an occupational disease of vital statisticians, seems to me grossly exaggerated. I think much of it would evaporate if the skeptics ever attempted to reassign the deaths attributed to heart disease. There are just too many of them. Either they represent a substantial reality or some other diseases represent a public health problem of much greater magnitude than anyone has previously suggested.

It must be granted that the difficulties in the reported death statistics are considerable, but few of them can be resolved by contemplation.

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In particular, rules of internal consistency for mortality statistics seem to me very slippery. If the mortality sex ratio is high among the white population and low among the Negro population, it may be simply that the death rate for arteriosclerotic heart disease *is* higher among Negro women than among white. We know that serious arteriosclerotic heart disease is very uncommon among middle-aged women unless they have diabetes or some similar metabolic defect. Conceivably such conditions are more common among Negro women than white. Mortality statistics certainly suggest that. Similarly, mortality sex ratios for arteriosclerotic heart disease are much lower in some countries than they are here. Does that mean those countries are reporting some other disease? Or does it mean that there is a real difference in the balance of factors controlling the appearance of the disease? The suggestion of Edward A. Lew of the Metropolitan Life Insurance Co. that there is a strong environmental component in the sex differentials for arteriosclerotic heart disease seems well taken. I think it is also true that there is an environmental component in the age differentials for this disease.

The question of what factors are involved in the development of coronary artery disease, which is the question that epidemiological studies in this field are concerned with, is a very vexed one. Numerous factors have been implicated, with or without evidence, but none of the really important issues has yet been settled. This is not peculiar to heart disease, however. All diseases may be said to involve a complex interrelation of factors, but the use of a simplified approach still has an obvious utility in the investigation of these factors. It is certainly not necessary that all of the critical factors be recognized or understood for a disease to be controlled, and it is conceivable that one or another of the presently considered factors may provide the key to the control of heart disease. Perhaps diet will prove to be that critical factor. Certainly, there is an increasing weight of evidence suggesting this possibility.

Unfortunately, it has become increasingly difficult to make epidemiological studies of diet in the American population. More and more people are dieting, think they are dieting, or think they ought to be dieting, and as a result their account of what they eat is apt to be confused and unreliable. In such circumstances the controlled nutrition experiments become more and more critical for our understanding of the role of diet. Currently, such experiments most frequently take the following form: some factor or factors, usually the kind of fat, are manipulated within a more or less carefully controlled regimen, while the remainder of the diet is kept the same or adjusted to maintain a constant caloric intake. The effect of this is measured by some index—total cholesterol or some other serum lipid, usually, since there is some evidence that the serum lipids are associated in a rough way with the risk of overt coronary artery disease.

In this kind of investigation the statistician can be of considerable assistance in designing economical inquiries and rationalizing their results. The usual result of these experiments is that the index goes up and down as the diet is altered, but there are no clear-cut criteria for deciding when the effect of one regimen has given way to the effect of another or (put another way) when we have reached an index level characteristic of a specified regimen. How do you decide when you have reached a steady state and when do you decide that this steady state is not transitory? Furthermore, there are individual differences in response, and while these are no doubt very important they are difficult to evaluate. At the moment this is a very complex but a very promising area of research.

Investigation of other factors in heart disease epidemiology can, at this stage, still be undertaken by field studies. The most serious problem in such studies is the low level of response. You are lucky to get two-thirds of any reasonable sample you select to participate in your study. No one seems to have turned up a way of improving the situation. Going to special groups, instead of to a general population sample, does not seem to help. Captive populations are much less cooperative than might be expected.

The problems of bias arising from nonresponse are certainly serious; and admitting them, unfortunately, does not make them any

easier. About all you can do that is worth doing is to find out as much about the nonrespondent group as possible. Prospective studies have some advantages in this regard, because there is a reasonable expectation that after a group has been followed for a time the initial bias will tend to diminish, but there is no gainsaying that reliable estimates of the prevalence of cardiovascular conditions in the general population are going to be hard to come by.

Unfortunately, the morbidity survey, which has proved useful in getting prevalence data for many diseases, has not worked out very well for the chronic diseases in general or for heart disease in particular. Contrary to some impressions it is neither cheap nor easy. What is worse it is exceedingly ineffective in identifying persons who would be considered to have heart disease on the basis of a careful clinical examination. No one will dispute that all available epidemiological techniques ought to be considered for the study of heart disease, but there is little advantage in dispersing our substance in a search for shortcuts. This is a real hazard: We are all impatient for answers to our questions about heart disease, and the routine clinical devices for accumulating pertinent epidemiological information are painfully slow and laborious. But here, as elsewhere, the slow and careful way may yet prove the quickest.

Shaw Promoted to Assistant Surgeon General

Dr. James R. Shaw, chief of the Public Health Service's Division of Indian Health, has been promoted to the grade of Assistant Surgeon General.

When the Public Health Service took over the Indian health program from the Department of the Interior in 1955, Dr. Shaw was made chief of the newly created Division of Indian Health. In that capacity, Dr. Shaw is responsible for the administration of medical and public health services for approximately 380,000 American Indians and natives of Alaska.

A career officer of the Public Health Service, Dr. Shaw has been commissioned since 1938. After assignments in Public Health Service hospitals and the U. S. Coast Guard, he became medical officer in charge of the U. S. Marine Hospital, Detroit, in 1949. In 1952 he was named chief of the Service's Division of Hospitals and served in that post until he began his duties in Indian health in 1953 with the Department of the Interior.

The Importance of WHO to Americans

SURGEON GENERAL LEROY E. BURNEY

I AM GRATEFUL to the National Citizens Committee for the World Health Organization for the opportunity to say something today about the importance of the World Health Organization to Americans. My remarks here will be rather in the nature of a personal statement—the impressions and reflections of one who is a relative newcomer to active association with WHO. Of course, my belief that WHO is important existed even before my first attendance at a World Health Assembly, the Eighth, held in the colorful setting of Mexico City in 1955. This conviction was accentuated by attendance in 1957 at the Tenth World Health Assembly in Geneva, the headquarters of the Organization. At this Assembly, I had the privilege of heading the United States delegation. Having to exercise responsibility during the Assembly for the effective and proper presentation of United States views is one of the best ways of necessitating a clear hard look at WHO programs and policies.

I did not find such a look disappointing. The World Health Assembly is genuinely an impressive meeting. The delegates, representing most of the countries of the world, give serious consideration to the world's pressing health needs and how they can be met, resulting in tangible decisions directly affecting the health of millions of human beings such as the decision to drive for eradication of malaria from the world. The Assembly provides unique opportunity to exchange views and to establish friendly relations with the health leaders of other nations. This is the essence of communication—both more ready interchange of technical information and more international understanding, which basically is understanding between individuals. A further development of the ties between Americans and health leaders in other countries is one among many reasons why I am delighted that the Assembly in May 1958 will be held in the United States.

Any realistic accounting of the benefits which Americans derive from United States membership in, and support for, WHO must include the following:

- Protection against importation of disease through almost universal application of the International Sanitary (quarantine) Regulations.
- Protection of the health of United States citizens traveling abroad through these quarantine measures and through control of diseases at their source.
- Stimulation of markets for United States products and lowering of prices of United States imports through reduction of the enormous drag of disease on economic productivity in many parts of the world.
- Making available to the United States, for application here, the latest health and medical advances in other parts of the world.
- WHO stimulation and correlation of such technical advances and of research.
- Friendship for, and in many cases direct acquaintance with, the United States among health leaders—leaders who are often influential in their own countries outside the field of health.
- WHO leadership in helping countries raise health levels and create more stable con-

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ditions of life as an essential part of the United Nations system.

Twin Contrasts

Hours could be spent in elaboration and illustration of any one of these points. I particularly wish to discuss some aspects of the last point—the basic importance of the World Health Organization in raising health levels and creating more stable conditions of life.

Today, we face staggering contrasts. In a few short decades, a minority of mankind, mostly in North America and Western Europe, have almost conquered major communicable disease and have prolonged the span of life so that now the problems and diseases of old age loom large before us. At this very same time, one-seventh of mankind suffer from trachoma, perhaps one-quarter are infested with intestinal parasites; one-tenth still suffer from malaria each year; the dysenteries, often fatal, especially in young children, are too prevalent for calculation.

This type of contrast symbolizes, in the field of health, the vast gap which separates the conditions of life in economically developed countries from those in the rest of the world. The medical science and the technology now exist to conquer these diseases, yet for only a minority of mankind have they been truly conquered. For the first time, peoples in nearly all economically underdeveloped areas are acutely aware that, for some, ill health is not a normal condition of life and, furthermore, that it need not be.

But there is another contrast. On the one hand, there is around the world an insistent demand for health. Consequently, the nations, working cooperatively through the World Health Organization, are beginning to be really successful in the mass applications of the recently developed modern knowledge of the means to health. These applications are ways to the kind of life where human potentialities can be realized; where hunger, disease, and ignorance do not drag man down in his ascent from levels of animal existence. Yet at this very same time, man has made vaulting strides, terrifyingly rapid, in developing the means of mass destruction. These are means which, when wrongly used, can serve the passions of hate, fear, and the lust to dominate.

These twin contrasts—between conditions of life for a minority of mankind and for a majority and between the technology of human welfare and the technology of destruction—define, in my opinion, the context in which we must now view the importance of the World Health Organization to Americans and to the world. The technical means to health and the organizational means by which nations cooperate to realize health fully form a priceless counterpoise to help balance these contrasts.

Areas of Common Interest

Thirteen years ago, the 73d annual meeting of the American Public Health Association heard an unusual address. Two years before the International Health Conference, it defined forcefully and incisively the basic meaning and value of an organization such as WHO. As so often in the evolution of public health programs, national or international, the Rockefeller Foundation, in the form of this address by its top official, seemed to be lighting a path for others to follow. In speaking on public health as an international problem, Dr. Raymond B. Fosdick, then president of the Foundation, declared:

"The community of nations has got to have a kind of intellectual and spiritual integration before it can be absolutely sure that the forces of violence are under control. Consequently there must be developed for international life new areas and techniques of cooperative action. . . . We need rallying points of unity, centers around which men of differing cultures and faiths can combine, defined fields of need or goals of effort in which by pooling its brains and resources the human race can add to its own well-being. . . ." Dr. Fosdick saw hope only "as we begin to build, brick by brick, in these areas of common interest where cooperation is possible and the results are of benefit to all. . . ."

Public health, he said, can be an important area of common interest, a rallying point of unity. This is my view, and I believe it was the view of the health experts directly responsible for founding the World Health Organiza-

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tion. All nations want health, and no nation in the process of gaining health takes it from another—rather, thereby, it helps to advance health everywhere.

This notable address listed activities which a new international health agency might profitably pursue. It is impressive for me, and hopeful, that the list was an accurate preview of WHO's present far-reaching activities: a worldwide epidemic intelligence system; the standardization of biological products; the organized exchange of public health personnel to broaden the technical outlook and stimulate the imagination of health officers; the supplementation of public health activity in countries where it is inadequate; the development of minimum standards of acceptable public health work that can be applied on a worldwide basis; the creation of expert committees and international conferences on special subjects.

These are all activities which, among others, WHO has inherited or initiated, expanded, and made markedly successful in 10 years. They represent the organized cooperative application, worldwide, of the swiftly developing modern technology of health—tangible interrelated action by most countries in the interests of all.

In September 1957, I had the opportunity to see for myself some of the progress in health being made in countries in the Pacific and Asian areas. I found fundamental changes taking place in these countries. Many of them, for example, are establishing spreading networks of rural health centers, which are the basic units of public health protection in that part of the world. During my all-too-short visit to that hospitable country, the Philippines, I saw several such centers. These rural centers, built largely by the efforts of the people in the villages, are so impressive that I confessed to my hosts that they are even better than many of our own here in the United States.

It is evident that in health most of the nations have indeed found an area of common interest. They have begun to build, brick by brick, expanding the techniques of cooperative action. In the context of today's world, this process, associated with international cooperation in other fields, such as education and agriculture, holds out hope. It is lessening, though slowly, the stark contrast in conditions of life; it is demonstrating incentive and ability to apply science for man's common benefit.

In viewing this essential value of the working of WHO, I have noticed how familiar many of WHO's techniques and modes of operation seem to be. Almost my whole professional life has been spent in the area of domestic intergovernmental health relations within the United States—as a State health official, working in cooperative relationships with Federal agencies, with other States, and with local and voluntary agencies; and as a Public Health Service official, in cooperative relationship primarily with the States, and with the same wide range of other organizations.

Through these effective working relations, we have built in the United States a true community of health effort.

On the plane of international intergovernmental health relations—the relations between WHO and member countries—the same trends are evolving. WHO's interrelationships with member countries seem familiar because, on reflection, they are in many respects quite similar to our relationships in technical matters between Federal and State health agencies. WHO's relationships with other United Nations specialized agencies and international voluntary organizations also remind me of our patterns of cooperation.

Techniques of a Free Society

The member nations of WHO are, of course, independent countries. Even though this is true, the pattern of technical relationships established between WHO and these countries contains the following elements which have a familiar ring to us.

WHO provides expert consultation and assistance to member nations. It develops and demonstrates public health methods which are new, or new to the nations concerned. It stimulates cooperative action among nations on problems requiring such action. And in annual regional and worldwide meetings, the evolving health needs and the future shape of health programs are determined. Through WHO, the nations are succeeding in building on a world scale many of the interrelationships

and techniques of cooperation which have proved so rewarding here—techniques of a free society.

These techniques of cooperation, indeed, involve not only WHO and national governments, but extend through them to a multitude of health experts and institutions within countries. The WHO Influenza Study Program is an example of great current interest. In this program, WHO has brought about organized cooperation between laboratories in many countries, which collect, study, and report on influenza virus strains. WHO gives small grants to a World Influenza Center in London and to the International Influenza Center for the Americas, operated by the Public Health Service in Atlanta, Ga., as focal points in this program. In the United States alone, 60 different laboratories cooperate.

Through the program, which also includes the essential participation of a WHO panel of experts around the world, there is constant worldwide watch on the appearance and spread of influenza epidemics and rapid identification of responsible strains. Owing in part to this WHO Influenza Study Program, we in the United States were alerted to the 1957 epidemic and were able to prepare for the invasion of the new strain through production of a protective vaccine.

The world, while now so interdependent, is still a large place. WHO makes use of a decentralized regional structure to an extent unique in international organization. I believe that this decentralization has considerably strengthened WHO as an instrument through which nations cooperate for health. Through the regional offices and regional committees, WHO is brought closer to the needs and governments of member countries, and they closer to WHO. When I recently attended the meeting in Hong Kong of the WHO Regional Committee for the Western Pacific, it was clear that the health leaders of that part of the world and the WHO staff are good friends and work closely together in defining needs and planning programs in health.

Moreover, the decentralized regional structure makes possible more flexibility and experimentation in the WHO programs. An example of a worthwhile experiment is the establishment of the Institute for Nutrition of Central America and Panama. Under the aegis of the Pan American Sanitary Bureau, the WHO Regional Office for the Americas, and supported largely by the Central American republics, this institute has attained a worldwide influence in nutrition.

Comparison with our own national experience, then, shows that WHO and the nations are evolving a pattern of cooperation along lines to which all Americans can wholeheartedly subscribe. In its sphere, WHO is becoming a "rallying point of unity." With the clearly defined need and goal of health in mind, men and nations of differing cultures and faiths are combining their efforts.

During the past year, some of the Soviet group of countries have resumed active membership in WHO. Even without their participation, WHO has already accomplished a great deal. The eventual character of renewed active membership by these countries remains to be seen. If, in the long haul, it turns out to be a real working together with other nations for health, this would considerably enhance the significance of WHO, as a pattern of cooperative action, applying the technology of human welfare. In such circumstances, the World Health Organization and associated international technical agencies might, given time, contribute more than we realize to bringing the forces of conflict into balance. It is our hope, and our imperative need, that this will be so.

Epilogue

I have given you some of the reflections of a relative newcomer to active concern with WHO affairs. After these reflections had been put on paper, I listened the other night to the President's address to the Nation on science in national security. In concluding his address, Mr. Eisenhower referred to the peaceful uses of science, naming specifically the contributions of science to healing as one of the most important products of the conquest of nature's secrets. Speaking for us all, he said that we will never cease to work for the day when the scientist can give his full attention, not to human destruction, but to human happiness and fulfillment. My theme today has been that

WHO represents this use of science, and that, insofar as it is successful, WHO is building a pattern of common interest and action which can strengthen the conditions of peace.

Those of us who have had opportunity to appreciate all facets of the importance of WHO have a responsibility to meet. The holding of the World Health Assembly in the United States in 1958 gives us added opportunity to meet that responsibility.

If the Eleventh World Health Assembly appears to the American people to be merely another meeting on a technical subject, we shall have missed the boat. If it leads to greater appreciation by our public of the world demand for health, of the effective moves to fill this demand with leadership by the World Health Organization, we will have partially grasped this priceless opportunity.

It seems to me, however, that taking full advantage of the opportunity means furthering public understanding of the role of WHO in the total world context, the context of sharp contrasts which I have tried to sketch today. The National Citizens Committee for the World Health Organization, as a voluntary association of leaders in health and public affairs, is best equipped to promote vigorously this fuller understanding of why the World Health Organization is actually important to Americans.

United States Host to Eleventh World Health Assembly

The World Health Assembly, the governing body of the World Health Organization, will hold its eleventh session in Minneapolis, Minn., beginning May 28, 1958. This will be the first session of the Assembly to be held in the United States.

Observance of the tenth anniversary of WHO is a special event of this year's meeting, and the Assembly delegates will participate in a commemorative session, May 26 and 27, preceding the regular session.

The World Health Assembly, composed of delegations from WHO's 88 member states, decides the Organization's policies, programs, and budget.

At Minneapolis, the Assembly will consider the annual report of the Director-General on the work of the World Health Organization during 1957. It will approve the program for 1959 and determine the amount of money needed to carry it out. The 1958 budget, mainly contributed by member states, is $13,500,000.

It will also elect 6 member states, each entitled to designate a person to serve on WHO's Executive Board of 18 health specialists. Six board members retire each year. The Executive Board makes recommendations to the Assembly and gives effect to its decisions.

The Director-General is appointed by the Assembly to serve as the chief technical and administrative officer of WHO, subject to the authority of the Executive Board. Dr. M. G. Candau is the present Director-General and is in charge of a staff of about 1,400 professional workers of 54 nationalities at WHO headquarters in Geneva and in the field.

In a decade of operation, the World Health Organization, working with national health services, has made substantial progress in controlling infectious diseases, training health workers, improving sanitary conditions, and in worldwide health activities of benefit to all countries.

Arthropod-Borne Encephalitis in 1956

E. RUSSELL ALEXANDER, M.D., and WALTER A. MURRAY, JR., M.D.

DURING 1956, the prevalence of arthropod-borne encephalitis varied considerably in the United States. Eastern equine encephalitis (EEE) returned in a small outbreak of human cases in southeastern Massachusetts, where 12 cases occurred, 8 of them fatal. Although the disease was widespread among horses and pheasants all along the Atlantic and Gulf Coasts from Massachusetts to Louisiana, only 3 other human cases were reported—2 from Maryland and 1 from Delaware. Western equine encephalitis (WEE) affected man and horses in a sporadic and sparse fashion over the western half of the country. St. Louis encephalitis (SLE) was the largest disease problem; there were several small foci in the West, with a large epidemic focus in the high plains of Texas, and an urban epidemic in Louisville, Ky., accounting for the majority of the cases.

The incidence of acute infectious encephalitis in man is reported routinely to the National Office of Vital Statistics, Public Health Service, by all States on a weekly basis. Because of the different criteria used by reporting States, this composite category embraces a crude collection of diseases of central nervous system infections including the arthropod-borne encephalitis group. The 1956 total of 2,624 cases listed according to State serves as a starting point for case appraisal (table 1). This number is the largest annual total reported for the disease category. Final totals have exceeded 2,200 cases only in 1954 and 1955. Marked annual variation in incidence for the years 1952 and 1956 is seen in figure 1, where sharp peaks in the even years reflect the known larger epidemic occurrence of the arthropod-borne encephalitides (*1*). Further statistical analysis of the 1956 report data has proved of limited usefulness in appraisal of the arthropod-borne encephalitides.

In 1956, encephalitis in horses produced 1,284 clinical cases, with 493 deaths, as reported to the U. S. Department of Agriculture (*2*). Cases and deaths listed by State in table 2 reflect reports from widely scattered endemic foci in large geographic areas of the West, as well as highly fatal cases concentrated on the eastern seaboard. Typical of the outbreaks were those in the Columbia River Basin in Washington, western Idaho, and adjoining counties of eastern Oregon. States reporting high mortality were localized in the Atlantic and Gulf Coast sections. That EEE was the cause of the high case fatality rate (80–90 percent) was proved by laboratories reporting isolations of the virus from these areas. In sections of known WEE prevalence, appraisal of reported cases is more difficult; this disease has a much lower mortality rate (15–35 percent), and therefore fewer brain specimens are submitted for laboratory diagnosis.

Dr. Alexander, formerly chief of the Surveillance Section, Epidemiology Branch, Communicable Disease Center, Public Health Service, is now with the department of pediatrics at the University of Chicago. Dr. Murray serves as assistant chief of the Surveillance Section of the Center.

Eastern Equine Encephalitis

Appraisal of the 15 human cases of EEE reported in 1956 resulted in the classification of 13 as confirmed and 2 as presumptive (table 1). The death of 10 of the patients and incapacitating sequelae in three survivors testify to the severity of this disease. A study of geographic distribution of cases shows a concentration in Massachusetts, where there were 12 cases, the

majority occurring in the southeastern part of the State in an area characterized by numerous fresh-water swamps. In 1938 the same area had 34 human cases of EEE, 25 of them fatal (*3*). The 1938 and 1956 outbreaks represent the largest and second largest, respectively, both for the State and for the Nation. One of the 1956 cases occurred in Delaware, and 2 in Maryland.

Seven laboratories within 10 Gulf and Atlantic Coast States reported a total of 42 isolations of EEE virus from horse brain specimens, the majority from New Jersey and Massachusetts (table 2). A wide range of seasonal occurrence is represented by isolations from Louisiana in May, and from New Jersey in early November. Although no virus isolations were reported from horses in Alabama and Florida, strong presumptive evidence of EEE is reflected in the reported mortality in excess of 90 percent (table 2).

Followup studies in 1956 on outbreaks of EEE in domestic pheasants resulted in 42 virus isolations from brain specimens submitted from Massachusetts, Rhode Island, Connecticut, and New Jersey.

EEE virus was isolated from 20 serum specimens collected from wild birds during ecologic studies in four States—Massachusetts, Rhode Island, New Jersey, and Louisiana (*4–8*). A few of the 20 virus isolations were from immature birds, and about equal numbers were from permanent-resident and migrant birds.

Natural isolations of EEE virus were obtained from 11 pools of arthropods collected in three States. From Massachusetts, five pools of unengorged *Culiseta melanura* were positive (*7*). Two pools of unengorged and one of engorged *C. melanura* collected in New Jersey, and two of engorged *Culex salinarius* collected in that State, yielded virus when tested in the Communicable Disease Center laboratory (*9, 10*).

These isolations incriminate *C. melanura* as the most probable vector of EEE, since it is the only species thus far to yield multiple isolations of virus from unengorged mosquitoes. This species was in high prevalence in both the Massachusetts and the New Jersey areas. Studies have indicated that their blood meals were primarily from birds and rarely, if ever, from man or horses. Therefore, this species may be the prime vector between birds and the occasional vector to humans or horses. It may be, however, that another species less often infected transfers the disease to these mammalian hosts.

Isolations of EEE virus were made from arthropods collected in Georgia, in July 1956 (*11*). For the first time, the virus was isolated from *Aedes mitchellae* and a pool of mixed species of insects from the genus *Culicoides*, and, for the second time, from *Anopheles crucians*. The separation of engorged specimens from the processed pools was not reported.

Western Equine Encephalitis

The sporadic and endemic occurrence of WEE in the western half of the United States during 1956 resulted in reports of 47 cases, 37

Data Collection

For the past decade, the Communicable Disease Center of the Public Health Service has conducted intensive field studies on the arthropod-borne encephalitides. Beginning in 1955, a systematic effort was made to collect data on the occurrence of these infections throughout the country. Sources included reports from the National Office of Vital Statistics of the Public Health Service, State and local health departments, academic and many other medical and veterinary virus diagnostic laboratories, the Disease Eradication Branch of the Department of Agriculture, and the Walter Reed Army Institute of Research. A report summarizing all the material was then distributed to contributors and others concerned with the control of these diseases.

This nationwide surveillance and continued mutual exchange of data resulted, in 1956, in five concurrent seasonal reports and an annual summary report, which are available on request to those interested in encephalitis research. By defining the pattern of arthropod-borne encephalitis in 1956, it is hoped that the public health importance of these diseases will be further clarified.

The present paper summarizes the information on the occurrence of arthropod-borne infections in 1956 and includes a summary of data for past years.

Classification Standards

In order to compare encephalitis activity in the different States from which varying amounts of data were submitted, standards were adopted for the classification of reported cases. These standards are flexible in recognition of the inevitable minor differences in technique between laboratories. The "confirmed" category includes all cases fulfilling the following criteria:

1. Isolation of virus.
2. Fourfold rise in titer of antibodies from acute to convalescent blood specimens.
3. A fourfold fall in titer during the convalescent stage.
4. A single high titer of complement fixing antibodies in a single convalescent serum collected from an area of proved concurrent epidemic.

The "presumptive" case includes all cases demonstrating any of the following:

1. A single high complement fixing antibody titer in an individual with clinical illness compatible with arthropod-borne encephalitis.
2. Case history of clinical encephalitis without any laboratory diagnosis in an area of proved concurrent epidemic.

The only criterion accepted as evidence of current animal infection (horses, pheasants, wild birds, mosquitoes, and other mammals) was isolation of virus.

of them confirmed (table 1). These cases, occurring in 10 States, showed a restricted, early seasonal occurrence, with a peak in mid-August. Analysis of age distribution revealed a concentration in infants (table 3). No fatalities were reported among either confirmed or presumptive cases.

Western equine encephalitis in horses was confirmed by reports of 2 isolations of the virus from brain specimens, 1 in Oklahoma and 1 in Washington. In the California encephalitis surveillance reports diagnoses were confirmed in fourfold, or greater, rises in antibody titer in clinical cases in horses (*12*). Including serologic and histopathological diagnoses, the U. S. Department of Agriculture lists another 33 instances of confirmation of diagnoses in 10 States (*2*). It was possible to accept as confirmed cases only those with virus isolation because of the difficulty encountered in the interpretation of serologic results of single blood specimens submitted without knowledge of the immunity status. The extensive use of vaccines, the difficulty in obtaining adequate history of their use, and the relatively sparse horse populations discourage reliance on reported clinical cases of WEE in horses. Characteristic case fatality of 25 to 35 percent was recorded in the clinical reports of the 1956 epidemics in the Columbia River Basin.

Eight species of wild birds yielded WEE virus in Rhode Island, New Jersey, and Louisiana, as reported by research groups who are working primarily on the ecology of EEE (*4–6*, *8*). For Rhode Island, the isolation of WEE from a chukar partridge is the first demonstration of this virus in the State, but in the other two States there were previous isolations.

The encephalitis surveillance program of the California State Department of Health reported isolations in 1956 of WEE from brains of four grey squirrels.

During 1956, WEE virus was isolated from 307 pools of mosquitoes collected in New Jersey, North Dakota, Texas, Nevada, Colorado, Idaho, Washington, and California, with the most isolations from the last four States. All isolations were from pools of *Culex tarsalis* except 2 in Texas which were from *Culex quinquefasciatus*, and 1 from *C. melanura* in an engorged pool in New Jersey.

Some measure of comparison with previous years is available from reports of the California State Department of Health. Mosquitoes collected in similar fashion from year to year in four county study areas reveal the following:

	1954	*1955*	*1956*
Pools tested	989	1,113	1,047
Pools positive	238	82	145
WEE virus	151	68	143
SLE virus	87	14	2

In terms of WEE virus recovery from mosquitoes, 1956 was not a light year, yet few human cases occurred.

St. Louis Encephalitis

The occurrence of 562 cases of SLE, 227 confirmed, makes this disease paramount among

Table 1. Encephalitis by State during 1956

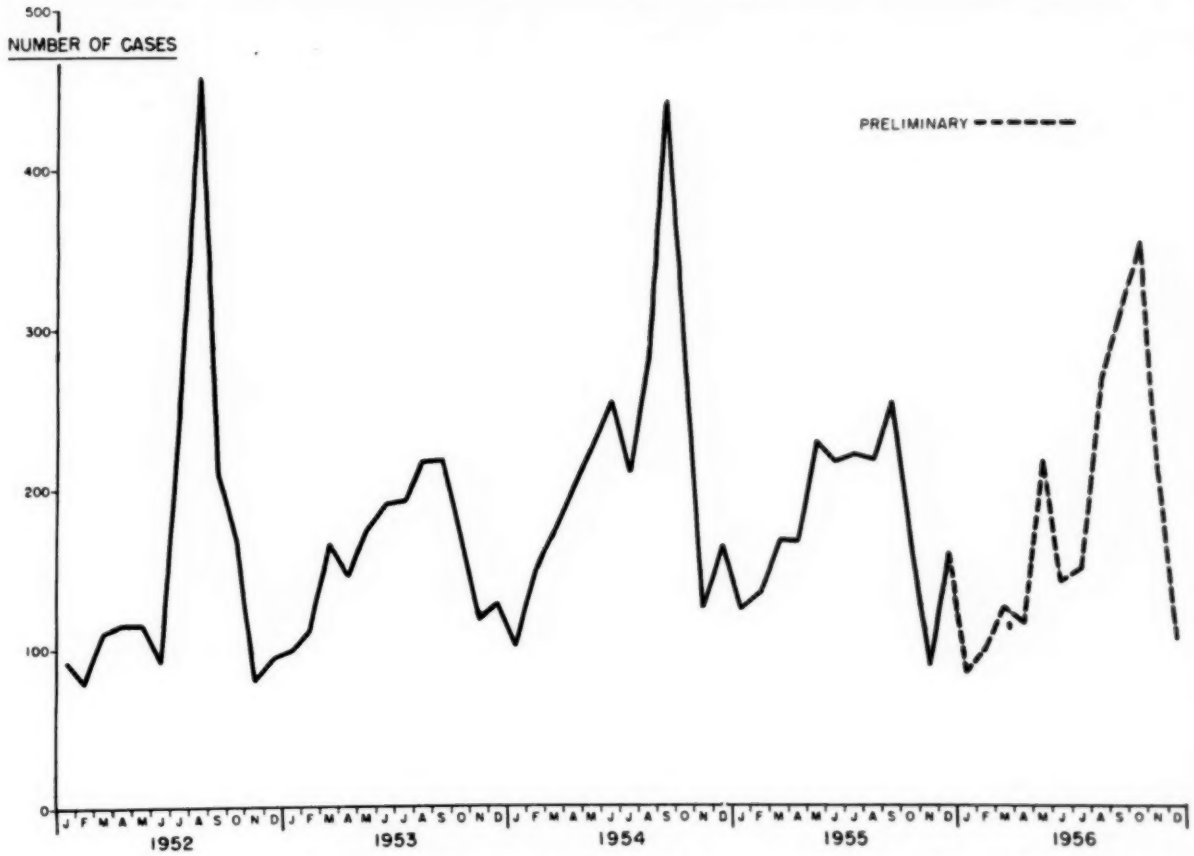
State	Report data [1]	Cases appraised as arthropod-borne encephalitis						Fatal cases
		EEE		WEE		SLE		
		Confirmed	Presumptive	Confirmed	Presumptive	Confirmed	Presumptive	
Maine	5							
New Hampshire	1							
Massachusetts	35	11	1					[2] 8
Rhode Island	5							
Connecticut	10							
New York	386							
New Jersey	34							
Pennsylvania	1							
Ohio	125							
Indiana	74					20	4	
Illinois	146							
Michigan	85							
Wisconsin	13							
Minnesota	8			2		2		
Iowa	24							
Missouri	15						2	
North Dakota	16							
South Dakota	14			1		2		
Nebraska	19							
Kansas	136				5	12	42	[3] 3
Delaware		1						
Maryland	27	1	1					[2] 2
District of Columbia	10							
Virginia	27							
West Virginia	4							
North Carolina	34							
South Carolina	21							
Georgia	17							
Florida	15							
Kentucky	145					64	56	[3] 14
Tennessee	27					1	3	[3] 1
Alabama	27							
Mississippi	19							
Arkansas	19							
Louisiana	4							
Oklahoma	16							
Texas	346			15	2	89	193	[3] 9
Montana	4							
Idaho	7			2	1	1	1	
Wyoming	3			2				
Colorado	66				1	24	33	[3] 3
New Mexico	7				1			
Arizona	7							
Utah	6					1		
Nevada	2						1	
Washington	29			1		3		[3] 1
Oregon	24					1		
California	559			14		7		
Total	2,624	13	2	37	10	227	335	41

[1] Reported Incidence of Notifiable Diseases in the United States, 1956, Morbidity and Mortality Weekly Report, Annual Supplement, vol. 5, No. 53, National Office of Vital Statistics, Public Health Service. No reported or appraised cases from Vermont.

[2] Eastern equine encephalitis.

[3] St. Louis encephalitis.

Figure 1. Reported infectious encephalitis cases in the United States, 1952–56.


NUMBER OF CASES
500
400
300
200
100
0
PRELIMINARY
J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D J F M A M J J A S O N D
1952
1953
1954
1955
1956

the arthropod-borne encephalitides in 1956 (table 1). Two large epidemics accounted for the majority of these cases. In the high plains area of the Texas Panhandle, a rural epidemic included over 250 cases of clinical encephalitis. Of these, 89 were confirmed in the laboratory as SLE and 15 as WEE, while the remainder were classified as presumptive. During an urban epidemic in Louisville, Ky., 110 people were affected. Other small epidemic foci were in Colorado, Kansas, Indiana, and southern Kentucky (at the Tennessee border), and sporadic cases were reported from 11 other States. Seven of 31 deaths were confirmed, 2 by virus isolation from brain tissue (table 1). Following the epidemic in Louisville, a 6 percent prevalence of complement fixing antibodies was found in serums from over 700 persons. From this, a crude estimate shows that the ratio of inapparent to apparent infections was more than 200 to 1.

There were 26 isolations of SLE virus from pools of mosquitoes reported in 1956, still sparse in comparison with reported isolations of WEE. All were made from pools of *C. tarsalis* collected from widely distributed foci in North Dakota, Kansas, Idaho, Colorado, Utah, Washington, and California. Considerable numbers of mosquitoes were collected in Texas and in the Louisville area but no SLE virus was obtained. No SLE virus isolations were reported from wild birds or other animals during that year.

Discussion

A composite of the total virus activity in 1956 for each of the three arthropod-borne encephalitides, as shown in figure 2, represents the sum of all evidence for activity of each specified virus in certain mammals, wild or domestic birds, and mosquitoes.

In some States the only evidence of EEE virus activity in an area was the excess mortality

in horses, but this evidence, although presumptive in nature, has proved remarkably reliable in the past. In addition, the report data on horses more clearly reflect seasonal occurrence than do data on human cases.

In 1956, the farthest extension southward of human cases of EEE was in Maryland, and the southernmost outbreaks in pheasants occurred in New Jersey. In contrast, during 1955, human cases of EEE were reported from Texas and Louisiana, and pheasant outbreaks from North Carolina and Florida. The seasonal occurrence of human cases was restricted to August and September in 1956; during 1955, onsets in an identical number of reported cases ranged from April to December. The 1956 epidemic in Massachusetts reached a peak during the first week of September, while the four cases reported from Massachusetts in 1955 had onset dates in late September and early October. This may have resulted from a late seasonal increase in mosquito prevalence attributed to the mid-September hurricane Diane. The epidemic peak in 1938 was reached shortly before a mid-September hurricane. Also in contrast with previous years, increased interest and improved laboratory techniques in 1956 have generated an impressive number of EEE virus isolations from wild birds and mosquitoes.

The distribution of WEE virus in 1956 followed expected patterns except for an extension into Rhode Island, as represented by a single isolation from a chukar partridge (fig. 3). For the second year this virus was active in New Jersey, where an impressive number of isolations were made from wild birds and from one pool of mosquitoes (*4–6,9,10*). These isolations demonstrate the extension of WEE virus activity to eastern shores and give fair warning signals for careful surveillance in these areas for both human and equine cases of this disease.

Again in 1956, as in recent years, an even more restricted interepidemic reporting of human and horse cases occurred, but substantial virus recovery from mosquitoes in several areas indicated that natural reservoirs were maintained and became widely dispersed.

Throughout much of the West, an abundance of the most efficient WEE vector, *C. tarsalis*, and the indications of highly susceptible human populations makes the disease a threat of considerable magnitude. This is especially true in rapidly developing irrigated areas, which may result in the introduction of a greater number of susceptible humans, more wild birds, and new breeding sites for *C. tarsalis*.

The irrigated areas of California contained a considerable number of pools of *C. tarsalis* with WEE virus in 1956. The fact that there were few human cases has been attributed by some to the effectiveness of the mosquito control program in the State, which, although not

Table 2. Reported encephalitis in horses, by State, in 1956

State	Reported cases[1]	Total deaths[1]	Number confirmed by virus isolation
Massachusetts	46	46	[2] 8
Rhode Island	9	9	[2] 2
Connecticut	1	1	[2] 1
New Jersey	48	46	[2] 11
Indiana	10	2	----
Illinois	7	----	----
Michigan	19	1	----
Minnesota	14	----	----
Iowa	15	10	----
Missouri	28	----	----
North Dakota	8	----	----
South Dakota	50	4	----
Nebraska	20	4	----
Kansas	24	4	----
Delaware	25	17	[2] 3
Maryland	33	33	[2] 3
Virginia	28	----	----
North Carolina	34	19	[2] 1
South Carolina	27	25	[2] 3
Georgia	44	32	[2] 8
Florida	107	87	----
Tennessee	11	11	----
Alabama	33	32	----
Mississippi	9	9	----
Louisiana	37	35	[2] 2
Oklahoma	36	14	[3] 1
Texas	133	----	----
Montana	35	----	----
Idaho	103	11	----
Wyoming	29	9	----
Colorado	25	5	----
New Mexico	5	----	----
Arizona	16	----	----
Utah	16	2	----
Nevada	8	2	----
Washington	69	21	[3] 1
Oregon	65	1	----
California	57	1	----
Total	1,284	493	[2] 42 [3] 2

[1] Data from Animal Disease Eradication Division, U. S. Department of Agriculture.
[2] Eastern equine encephalitis.
[3] Western equine encephalitis.

Table 3. Age distribution of encephalitis cases under age 10

Age group (years)	Eastern equine encephalitis			Western equine encephalitis			St. Louis encephalitis								
							Mountain and Pacific			East Central			West Central		
	C	P	Total	C	P	Total	C	P	Total	C	P	Total	C	P	Total
0–1	2	----	2	9	----	9	------	1	1	----	----	------	1	19	20
1–2	1	----	1	2	----	2	------	------	------	----	----	------	----	4	4
2–3	1	----	1	----	----	------	------	------	------	----	2	2	1	6	7
3–4	1	----	1	----	----	------	1	1	2	----	1	1	1	11	12
4–5	1	1	2	2	----	2	1	------	1	1	----	1	1	6	7
5–6	----	----	------	1	----	1	3	3	6	2	----	2	----	3	3
6–7	1	----	1	3	1	4	------	------	------	----	----	------	----	6	6
7–8	1	----	1	----	----	------	1	------	1	1	----	1	----	4	4
8–9	1	----	1	2	----	2	1	------	1	----	----	------	2	3	5
9–10	1	----	1	1	----	1	3	------	3	----	----	------	1	1	2
Total	10	1	11	20	1	21	10	5	15	4	3	7	7	63	70

C=confirmed; P=presumptive.

reducing the reservoir of the virus in nature, is effective in preventing transmission to man. Another point of view holds that the incidence in humans is not directly related to the virus infection rate in mosquitoes, that it has direct relation to the immunity status of the exposed population. Further evidence will be needed to clarify this point.

Although sizable widespread outbreaks of SLE were recorded in 3 States and sporadic cases in 11 others, activity of this virus was not described outside previously known areas (fig. 3). For an analysis of SLE characteristics in different areas, cases were arranged into the following geographic divisions: East Central States (Indiana, Kentucky, and Tennessee), West Central States (Minnesota, Missouri, South Dakota, Kansas, and Texas), and Mountain and Pacific States (Idaho, Colorado, Utah, Nevada, Washington, Oregon, and California).

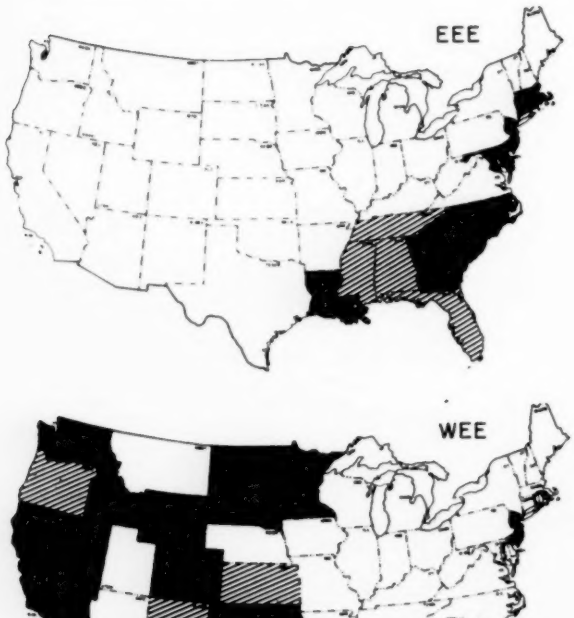
A study of the sex distribution of cases in these areas reveals markedly equal incidence in males and females in West Central and Mountain-Pacific States (males, 221; females, 220), but a notable predominance of cases in females in the East Central States (males, 49; females, 99). This is a reflection of the data from Louisville, but this same predominance among females was not found in a recent serologic survey.

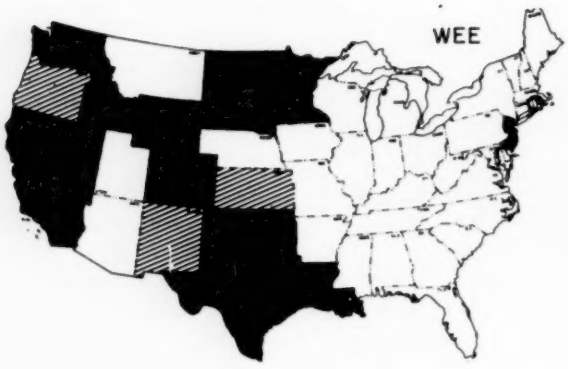
Marked contrasts occur in age distribution of cases of SLE in these areas (fig. 4). In the East Central States there is a paucity of cases among children and young people, with peak incidence in the 40- to 70-year age groups. This pattern is typical for 1933 and for the past 2 years. In this area the epidemiological characteristic most likely to suggest SLE is the initial report of seasonal encephalitis in older persons. In sharp contrast, epidemiologists in western States report a typical preponderance of SLE cases in the under-10-year age group, but with a weighting toward the upper level of this age bracket. It also contrasts sharply with the age pattern for WEE and EEE, both of which most frequently affect infants (table 3).

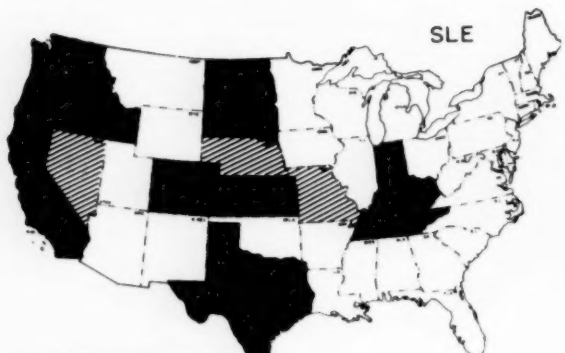
The West Central States have a larger proportion of presumptive SLE cases, as reported from extensive occurrences in Texas and Kansas (fig. 4). In the light of WEE virus activity in these areas, some cases classified as presumptive on clinical grounds in these major SLE epidemic areas actually may have been WEE. This might account for some of the cases in the under-10 age group, and particularly those in infants (table 3). To ascertain the true distribution of SLE, incidence figures should include only confirmed cases. To determine whether the age distribution pattern for SLE in the West Central States adheres to the pattern in the Mountain and Pacific States or to that in the East Central States, or a mixture of the two, requires more exact data.

The seasonal occurrence in these three geo-

Figure 2. Geographic distribution of arthropod-borne encephalitides in man and animals in the United States, 1956.







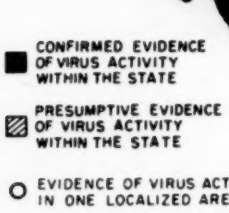
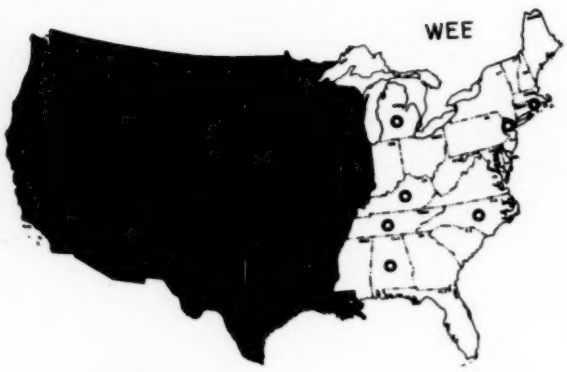
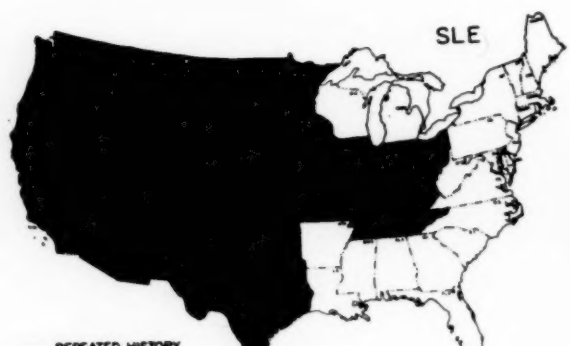
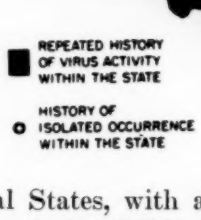

CONFIRMED EVIDENCE OF VIRUS ACTIVITY WITHIN THE STATE
PRESUMPTIVE EVIDENCE OF VIRUS ACTIVITY WITHIN THE STATE
EVIDENCE OF VIRUS ACTIVITY IN ONE LOCALIZED AREA

Figure 3. Historical pattern of arthropod-borne encephalitis virus activity, by State, through 1956.







graphic areas reveals a situation similar to that in the age distribution study (fig. 5). Peak occurrence was in August in the Mountain-Pacific States following the August peak of WEE. Also consistent with previous reports was the September peak for SLE in East Central States, with abrupt cessation of activity even before killing frosts. In confirmed cases from West Central States, SLE activity is faithfully reflected in the late August peak, but the addition of presumptive cases shifts the curve to a later period. As with the age distribution data, this again is a dilution of the analysis with presumptive cases, which in-

Figure 4. Age distribution of St. Louis encephalitis in 1956, by region.

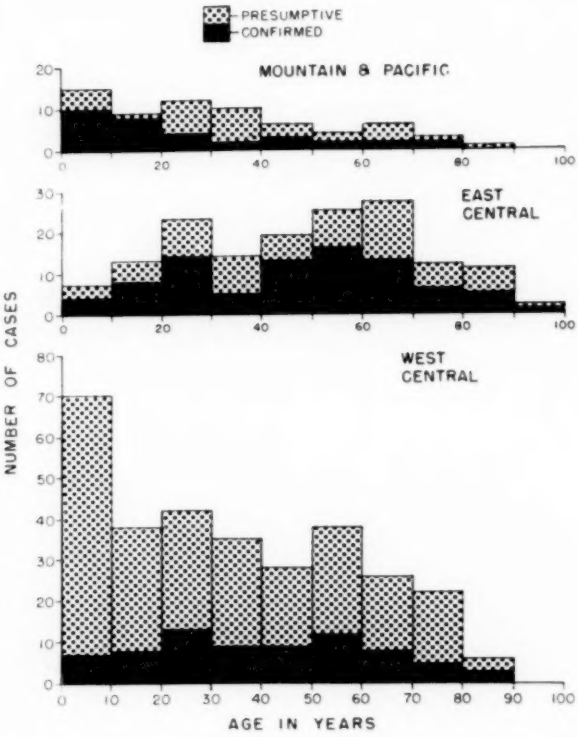
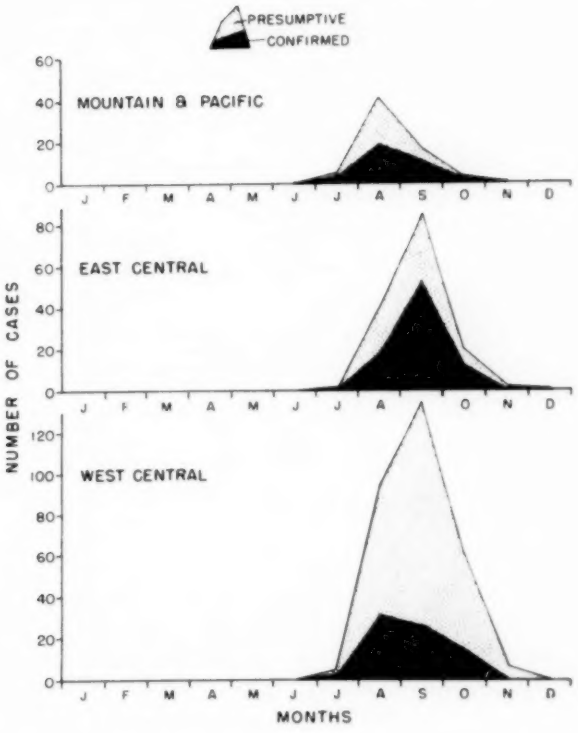


Figure 5. Monthly case occurrence of St. Louis encephalitis in 1956, by region.



cluded many with date of report rather than date of onset.

A problem concerned with arthropod-borne encephalitis illnesses is the severity of sequelae after apparent and, possibly, inapparent infections. In certain States, information on sequelae is being obtained as a part of research studies. A longitudinal clinical followup study in California has reported that permanent sequelae are mainly confined to those persons who were in the under-10 group at the time of infection, and that the frequency of severe sequelae appears to be greatest in infants, particularly in infants under 3 months of age (*13*).

It is interesting to speculate on the possible explanations of the differing epidemiological characteristics in these two areas. Two contributing factors may be operative. First, SLE in Mountain and Pacific States probably is transmitted primarily by *C. tarsalis*, whereas in Eastern Central States the vector is probably *Culex pipiens* or *C. quinquefasciatus*. The characteristics of these species regarding field or house environment may be important, and it is possible that the continued passage of the same virus through species with different incubation periods may lead to minor strain variations. Some laboratory investigations would suggest that such strain differences can be seen in virus isolated in those two geographic areas, although there is no antigenic differentiation.

The second factor to consider is the accumulating knowledge on the immunity of resident populations in the two areas. In certain endemic locations in the West there are significantly higher neutralizing antibody rates to SLE, with little history of clinical disease, than in comparable populations in the East Central States. Although the explanation for the differences in age distribution is not clear, and it is probably more complex than it appears, the fact that there is a significant difference between the two areas is important to record and study.

Studies of the hidden public health problems which may be presented by these diseases are in progress. Increased emphasis on diagnosis of aseptic meningitis may help elucidate cases that are often reported as viral encephalitis.

In many laboratories, work is advancing on the problems of the unidentified viruses, of isolated viruses whose potential for causing disease is unknown, and of disease agents that react with serums of patients from past epidemics of "unidentified encephalitis." Likewise, the problem of encephalitis of unknown etiology might be attacked by better analyses of the diseases reported as encephalitis, particularly the parainfectious encephalitides.

A real problem today resides in arthropod-borne encephalitides that are not now seen in the United States but might be imported. For example, in 1956 an illness in an individual, who became sick on arrival in California from Okinawa, was later diagnosed as Japanese B encephalitis, and in 1955 a case of Venezuelan encephalitis was reported in a laboratory worker in Washington, D. C. The public health hazard in such instances is the possibility of mosquitoes becoming infected, permitting survival and propagation of the virus locally. This, plus the possible introduction of infected mosquitoes, points up the need for increased knowledge and surveillance of arthropod-borne viruses by those responsible for the public health.

Summary

By charting the pattern of arthropod-borne encephalitis during 1956 through surveillance activities, it is hoped the public health importance of these diseases will be further defined.

The increased incidence of the arthropod-borne encephalitides in 1956 was characterized by:

The sporadic occurrence of EEE in horses throughout the Atlantic and Gulf States, with restriction in humans to 12 cases in southeastern Massachusetts, 1 in Delaware, and 2 in Maryland. Substantial virus isolations were recorded from mosquitoes and wild birds in Massachusetts and New Jersey.

Western equine encephalitis occurred diffusely in nature, as reflected by recovery of virus from mosquitoes. Although it failed to spill over into man and horses in epidemic fashion, it still remained a severe disease threat in irrigated areas of the West.

St. Louis encephalitis was the main contributor to the high incidence of reported acute infectious encephalitis. Although the virus was difficult to recover from participants in the natural cycle, the disease was readily apparent in a large rural epidemic in Texas and in three smaller foci in Kansas, Colorado, and Indiana. SLE reappeared in an urban epidemic in Louisville, Ky., for the first time since 1937.

Numerous public health problems, those stemming from encephalitis of unknown etiology, for example, and the possible importation of foreign encephalitides require further study.

REFERENCES

(1) Ferguson, F. F.: Biological factors in the transmission of American arthropod-borne virus encephalitides. Public Health Service Pub. No. 372. Pub. Health Monogr. No. 23. Washington, D. C., U. S. Government Printing Office, 1954.

(2) Hourrigan, J. L.: Summary report on the incidence of infectious equine encephalomyelitis in the United States in 1956. Washington, D. C., U. S. Department of Agriculture, Animal Disease Eradication Division, 1957.

(3) Feemster, R. F.: Equine encephalitis in Massachusetts. New England J. Med. 257: 701–704, Oct. 10, 1957.

(4) Kissling, R. E.: Host relationship of the arthropod-borne encephalitides. Presented at New York Academy of Science-U. S. Communicable Disease Center Conference on Animal Disease and Human Health, September 11, 1957. To be published.

(5) Stamm, D. D.: Studies on the ecology of equine encephalomyelitis. Presented to Joint Laboratory Section and Conference of Public Health Veterinarians, American Public Health Association, November 13, 1957. To be published.

(6) Sussman, O., and Cohen, D.: Equine encephalomyelitis in horses, pheasants and wild birds. Presented at 44th annual meeting, New Jersey Mosquito Extermination Association, March 1957. In press.

(7) Feemster, R. F., Wheeler, R. E., Daniels, J. B., Rose, H. D., Kissling, R. E., Hayes, R. O., Alexander, E. R., and Murray, W. A.: Field and laboratory studies on equine encephalitis. To be published.

(8) Dardiri, A. H., Wheetley, G. H., and Fry, D. E.: The isolation of eastern equine encephalomyelitis virus from brains of sparrows. J. Am. Vet. M. A. 130: 409–410, May 1, 1957.

(9) Burbutis, P. P., and Jobbins, D. M.: *Culiseta melanura* and eastern equine encephalomyeli-

tis in New Jersey. Presented at 44th annual meeting, New Jersey Mosquito Extermination Association, March 1957. In press.

(*10*) Chamberlain, R. W.: Vector relationships of the arthropod-borne encephalitides in North America. Presented at New York Academy of Science-U. S. Communicable Disease Center Conference on Animal Disease and Human Health, September 11, 1957. To be published.

(*11*) Karstad, L. H., Fletcher, O. K., Spalatin, J., Roberts, R., and Hanson, R. P.: Eastern equine encephalomyelitis virus isolated from three species of diptera from Georgia. Science 125: 395–396, Mar. 1, 1957.

(*12*) California State Department of Public Health: Surveillance report. Nos. 1 through 11. Berkeley, Calif., 1956.

(*13*) Finley, K. H., Longshore, W. A., Jr., Palmer, R. I., Cook, R. E., and Riggs, N.: Western equine and St. Louis encephalitis. Preliminary report of a clinical follow-up study in California. Neurology 5: 223–235, April 1955.

WHO Tenth Anniversary Publications

On the occasion of the tenth anniversary of the World Health Organization, the agency has prepared a variety of information materials, described briefly in the following list. Unless otherwise indicated, all items are available at the Office of Public Information, Pan American Sanitary Bureau, Regional Office for the Americas, 1501 New Hampshire Ave., NW., Washington, D. C.

• A series of basic fact sheets on WHO structure and programs, issued in quantity about every 2 weeks.

• A folder entitled "WHO, What it is, What it does." The last page presents in tabloid form, "Ten Years of World Health."

• An illustrated brochure, "Ten Steps Forward." It contains 40 pages of text written by a well-known English science writer and 24 pages of photographs. The publication is sold for 50 cents through the Columbia University Press, International Document Service, 2960 Broadway, New York 27, N. Y. Glossy prints may be obtained from the Pan American Sanitary Bureau.

• A 500-page book in commemoration of the tenth anniversary, covering all phases of WHO. At the end of May 1958 the book will also be available at the Columbia University Press.

• A book on WHO and the public health problem in the Americas and Western Africa. Written by Murray Morgan, a reporter from the State of Washington, it is published by Viking Press under the title "Doctors to the World." Available in May 1958 at regular bookstores.

• *World Health* magazine, formerly the WHO newsletter, special anniversary edition including 80,000 copies in English. The publication will be distributed in May and June 1958.

• A tenth anniversary film, in black and white, running for about 55 minutes, and especially tailored for television showing.

• A tenth anniversary set of 12 photographs entitled "World Health Advances." Each is supplied with an explanatory caption and packed in a large envelope.

• "Pictures of Health," a small booklet using the photographs which appear in the picture set. It is designed for use as a throwaway complementary to the WHO folder.

St. Louis Encephalitis in 1933

observations on epidemiological features

By L. L. Lumsden, M.D.

L. L. Lumsden, 1875–1946, a self-styled "shoe-leather" epidemiologist, was a pioneer in indicting the mosquito as a vector of encephalitis. A Public Health Service officer from 1898 to 1939, Lumsden blended rugged realism with an imagination that conceived of the Public Health Service as a logical nucleus for national coordination of State, county, and municipal health activities. He also organized at Yakima, Wash., a full-time county health service, setting a national pattern for local health departments.

THESE OBSERVATIONS on the epidemiology of epidemic encephalitis lethargica are based on findings in the course of studies authorized in a letter dated September 14, 1933, from the Surgeon General of the Public Health Service. The studies included field surveys in St. Louis City, St. Louis County, Independence, Jackson County, Kansas City, Sedalia, Jefferson City, and Columbia in Missouri, East St. Louis, Collinsville, and Chicago in Illinois, and Louisville and Jefferson County in Kentucky.

Intensive studies, including home visits and collection of individual epidemiological case histories, were made in Independence and in Blue Township in Jackson County. In the collection of detailed data in that city and township able assistance was furnished by Dr. W. F. Lunsford, statistician, Missouri State Board of Health, and by the staff of the Jackson County Health Unit. In the other places visited the studies made by the writer were of a general rather than an intensive detailed character. In the St. Louis region, where next after the Independence region the incidence of the disease in proportion to population was highest and where the large majority of the cases in the epidemic occurred, the intensive detailed studies were made by other officers of the Public Health Service, and their findings, presumably, will be the subject of an exhaustive detailed report.

Chronology and Geographic Distribution

From such evidence as has been obtainable, it appears that the earliest cases of encephalitis lethargica definitely diagnosed in the Missouri epidemic of 1933 had their onset of pronounced symptoms in the last day or two of July and were in a few persons residing in widely separated homes in rural parts of St. Louis County, 10 to 15 miles out from the limits of St. Louis City. Soon thereafter, the disease developed in epidemic rate among the residents of the thickly built-up zone ranging from 1 to 5 miles

Historical Note

In 1933 an unprecedented outbreak of human encephalitis occurred near St. Louis, Mo. When investigations were started by local, State, Federal, and other research workers, it was not known whether a virus, bacterium, or toxic chemical agent was involved. The mode of transmission was equally obscure. During the course of the epidemic, a virus was isolated and characterized—the first time that the etiological agent of any acute epidemic encephalitis of man had been identified. The virus of western equine encephalitis had been under study in the laboratory only since 1930; the virus of eastern equine encephalitis was being studied concurrently with the St. Louis virus and its isolation was also reported in 1933. These were known only as equine diseases. The role of mosquitoes in spreading any of these viruses was not known.

Into this abyss of ignorance and into the midst of a raging epidemic, the Surgeon General of the Public Health Service assigned Medical Director L. L. Lumsden for epidemiological studies. Two conflicting views developed as to the mode of spread of the St. Louis agent. A majority group, influenced by previous epidemiological studies on poliomyelitis and lethargic encephalitis, favored human to human transmission, while a minority viewpoint, vigorously presented by Lumsden, favored insect transmission.

It is to Lumsden's credit that, after a careful survey of the situation, he reached a sound hypothesis as to the mode of transmission of St. Louis encephalitis, a hypothesis which has proved applicable to other virus encephalitides in North America. This has been abundantly proved by later work. For this reason, Lumsden's unpublished report of 1933, with its sound conclusions as well as its deficiencies, is printed in full at this time.

The ease and frequency with which the viruses of St. Louis, western equine, and eastern equine encephalitis are now isolated from nature and manipulated in the laboratory indicate progress in this field which must be credited largely to a small group of devoted workers who have continued inquiries when there were no epidemics and when there was little interest or support for such research. However, if we were today confronted with another episode of encephalitis lethargica such as the 1933 St. Louis epidemic, it is debatable if its course could be materially altered, the mortality rates suppressed, or the sequelae ameliorated.

—WILLIAM L. JELLISON, *parasitologist, Rocky Mountain Laboratory, Public Health Service, Hamilton, Mont.*

in width in St. Louis County and adjacent to and to the west, north, and south of the city, and also among residents of the outskirts of the city of St. Louis lying next to the affected county zone.

Senior Surgeon J. P. Leake states, "during the early part of the epidemic, the rate of incidence in St. Louis County was 11 times that in St. Louis City." Eventually cases of the disease were reported from every ward of the city, but for the whole period of the epidemic (approximately August 5 to October 14) the rate of incidence was very much higher among residents of the outlying western wards next to the county line than among residents of the "downtown" wards, although the latter include some of the most densely populated areas of the city. According to reports as of October 10, the rate of incidence in the two large wards adjacent to the Mississippi River and farthest downtown from the heavily affected county zone was only about one-fifth of that in some of the outlying wards adjacent to the county zone. For the whole period of the epidemic, the rate of incidence, according to official reports, in St. Louis County was nearly four times that in St. Louis City.

If the rates of incidence of encephalitis in the different areas of St. Louis City were, as appears probable, even roughly or generally in inverse proportion to the distance from the St. Louis County zone of high prevalence, such occurrence taken alone would appear to be of some epidemiological significance, and, perhaps, would become of more epidemiological significance if considered in connection with

the direction of prevailing winds, with main currents of travel by persons, and with other possible factors in the spread of disease.

According to records of the State board of health, the reports of cases of encephalitis lethargica, by weeks, in the cities and counties of Missouri in the period August 1 to October 21, 1933, were as indicated in table 1 (*1*).

From these records it appears that the epidemic began and also reached its height in the St. Louis region about a week or two before it did in the Independence (Jackson County) region, but that the marked decline in the epidemic occurred somewhat sooner in the Independence region than it did in the St. Louis region. It is interesting to note that of the two

Table 1. Number of cases of encephalitis reported, by weeks, and case incidence, 1933

Location	Week ended—											Total cases	Population [1]	Case rate, 100,000 population
	August			September					October					
	12	19	26	2	9	16	23	30	7	14	21			
City														
St. Louis	3	15	40	104	107	104	62	45	41	14	13	548	821, 960	66
Independence [2]												(63)	15, 296	421
Kansas City	0	1	2	5	4	0	0	0	0	0	4	16	399, 746	4
St. Joseph	0	0	4	10	8	9	2	3	5	3	0	44	80, 935	54
Jefferson City	0	0	0	0	0	0	0	0	0	0	0	0	21, 596	0
Sedalia	0	0	0	0	0	0	0	0	0	0	0	0	20, 806	0
Springfield	0	0	0	0	0	0	0	0	0	0	0	0	57, 527	0
Joplin	0	0	0	0	0	0	0	0	0	1		1	33, 454	2
Columbia [3]												(?)	14, 967	46
County														
St. Louis [4]	33	67	95	96	91	78	33	22	10	7	3	535	211, 593	252
Jackson [5]	0	0	9	28	42	15	8	13	5	2	2	124	70, 708	175
Boone [6]	0	0	0	0	1	1	2	0	2	1	2	9	30, 995	29
Audrain	0	0	0	0	0	1	0	0	0	0	0	1	22, 077	4
Bates	0	0	0	0	0	0	1	0	0	0	0	1	22, 068	4
Buchanan	0	0	0	0	0	2	0	0	0	0	0	2	98, 633	2
Carroll	0	0	0	0	0	0	0	0	1	0	0	1	19, 940	5
Cass	0	0	0	0	0	0	0	0	0	1	0	1	20, 962	4
Clay	0	0	0	1	0	0	0	0	0	0	0	1	26, 811	3
Clark	0	0	0	0	0	2	1	0	0	0	0	3	10, 254	29
De Kalb	0	0	0	0	1	0	0	0	0	0	0	1	10, 270	9
Dunklin	0	0	0	0	0	0	0	0	0	1	0	1	35, 799	2
Franklin	0	0	1	0	0	0	0	0	0	0	0	1	30, 519	3
Greene	0	0	0	0	0	2	0	0	0	0	0	2	82, 929	2
Henry	0	0	0	0	0	0	0	0	0	1	0	1	23, 931	4
Hickory	0	0	0	0	0	0	1	0	0	0	0	1	6, 430	15
Jefferson	0	0	0	0	0	1	2	0	0	0	0	3	27, 563	10
Knox	0	0	0	0	1	0	0	0	0	0	0	1	9, 658	10
LaFayette	0	0	0	0	1	0	0	0	0	0	0	1	29, 259	3
Lawrence	0	0	0	0	0	0	0	0	1	0	0	1	23, 774	4
Montgomery	0	0	0	1	0	0	0	0	0	0	0	1	13, 011	7
Morgan	0	0	0	0	0	0	0	0	1	0	0	1	10, 968	9
Nodaway	0	0	1	0	0	0	0	0	0	0	0	1	26, 371	3
Phelps	0	0	0	0	0	1	0	0	0	0	0	1	15, 308	6
Polk	0	0	0	0	1	0	0	0	0	0	0	1	17, 803	5
St. Charles	0	0	0	0	0	0	1	2	0	1	0	4	24, 354	16
Saline	0	0	0	0	0	0	1	0	0	0	0	1	30, 598	3
Shelby	0	0	0	0	1	2	0	0	0	1	0	4	11, 983	33
Stoddard	0	0	0	0	0	1	0	0	0	0	0	1	27, 452	3
Total for State	36	83	152	245	258	219	114	85	66	33	24	1, 315	2, 458, 308	[7] 36

[1] United States census, 1930.
[2] Number of cases comprised in figures for Jackson County.
[3] Number of cases comprised in figures for Boone County.
[4] Outside St. Louis City.
[5] Excluding Kansas City, including Independence.
[6] Including Columbia.
[7] For whole State, including counties for which no cases were reported.

regions of the State which were most heavily affected, one (St. Louis) is on the east border of the State and the other (Independence) is near the west border about 300 miles from St. Louis and that, with the exception of Columbia in Boone County, there were very few cases reported in the cities and the 7 counties along the main lines of travel between St. Louis County and Jackson County. In the three counties adjacent to St. Louis County, with a total population of 82,436, only 8 cases were reported—4 in St. Charles, 1 in Franklin, and 3 in Jefferson—and in none of the 7 counties along the main line of travel between St. Louis and Jackson County was a case reported.

Within the period August 1 to October 21, not a case was reported in either Jefferson City, with a population of 21,596, or in Sedalia, with a population of 20,806. Both of these cities are on the main current of travel between St. Louis and Kansas City. The State Fair, which was attended by many persons from the St. Louis and Independence regions, was held at Sedalia August 12 to 19, inclusive, when the period of causation of the disease in the St. Louis region was, presumably, at its height. Columbia and Independence, which cities are somewhat offside from the main current of travel between St. Louis and Kansas City, were stricken—the former moderately and the latter very severely. The incidence in Independence and in the zone about 6 miles wide (in Blue Township, Jackson County) between that city and Kansas City was much higher than the rate in St. Louis City and County. As nearly as the population can be estimated, the incidence in the area (of Blue Township) lying between Independence and the northeast section of Kansas City was 1 case to about 125 of population. In Jackson County outside Independence, Blue Township, and Kansas City, not a case was reported.

In Kansas City, with a population of 399,746, only 16 cases were reported to the State board of health between August 1 and October 21. The records of the Kansas City Health Department, however, showed on September 28 that 33 cases developing in the city had been reported to that department since August 1. It is exceedingly doubtful that as many as 100 cases actually occurred among residents of Kansas City during the epidemic. At even such liberal estimate the case incidence in that city would have been only 1 to about 4,000 of population. It appears that a large proportion of the cases developing in Kansas City were in persons residing in the northeastern section of the city near the Jackson County (Blue Township) line.

In East St. Louis, Ill., with a population of 74,347, directly across the river from St. Louis, Mo., and connected therewith by bridges over which there is a constant current of traffic, only 3 local cases were reported between August 1 and September 25, but in Collinsville, Ill., a scattering village of 9,235 population located about 6 miles east of the city limits of East St. Louis, 4 local cases were reported within that period.

In Chicago, Ill., with a population of about 3,500,000, only 3 cases of encephalitis lethargica among residents were reported between August 1 and September 29. The number of cases reported in 1932 was 21 and the number reported in the period January 1 to August 1, 1933, was 6. In view of the tremendous amount of traffic between Chicago and St. Louis and Kansas City, the fact that Chicago was not reached by the epidemic is significant.

If encephalitis lethargica has an incubation period of 1 or 2 weeks, or more, as is assumed—apparently without definite reasons—by some observers, it is remarkable that a considerable number of persons while incubating the "infection" did not go from the epidemic areas to Chicago and have the onset of the disease while there. If the disease is caused by an infection which is transmitted either through personal contact or by flying insects, such as mosquitoes, which will travel by train, Chicago's complete escape from the epidemic would be difficult to understand, unless the incubation period (if any) of the disease is very short and the "infection," if conveyed by insects, is harbored by the "carrier-insects" for only a short period—less than 12 or 24 hours.

In Louisville, Ky., with a population of 307,745, located about the same distance by automobile or train travel from St. Louis as is Chicago, 28 cases of, with 9 deaths from, encephalitis lethargica were reported among residents of the city between August 1 and Septem-

ber 21, 1933. In addition to these, about 20 suspected cases were reported. Judging by the records of the city health department and the findings in the survey of the situation, the probability is that approximately 60 cases of the disease developed among the residents of Louisville in the period August 10 to October 10. A large majority of the cases were among persons residing in one or the other of two outskirts of the city about 6 miles apart.

Why was there such a distribution of the disease in the epidemic? Why did the incidence become less as the densest centers of population farthest away from the affected suburban zones were approached in St. Louis City and Kansas City and Louisville? Why did not the disease follow the main currents of human travel? Why did Jefferson City, Sedalia, and Chicago entirely escape? Why did Columbia have a fairly high prevalence? Why did Collinsville have a rate of incidence of the disease 10 times that of East St. Louis? Why were the cases in Louisville mainly in persons residing in one or the other of two outlying sections of the city about 6 miles apart? The answers to these questions should lead to sound epidemiological conclusions as to the mode of spread of the disease.

Judging by the reports recently received, it appears that with the advent of cool or cold weather in each of the heavily affected areas, the disease promptly ceased to prevail in epidemic proportions—in the Independence region somewhat before it did in the St. Louis region, although the epidemic began in the former region 2 weeks or more later than it did in the latter. The decline or the practical termination of the epidemic with the advent of cool or cold weather may be, of course, entirely coincidental and present no relationship of cause and effect; but to our elder epidemiologists it is somewhat remindful of the observations on yellow fever incidence in the days prior to 1900 when that disease, too, was a "mysterious malady."

General Considerations

The high rate of incidence of encephalitis lethargica in persons in the older age groups, the rapid spread of the disease over large areas in the regions affected, and all of the other general epidemiological features suggest that in this epidemic in Missouri we were dealing with a new or a comparatively new disease or a new type of an old disease. At the beginning of these studies the nature of the causative agent of the disease was entirely unknown.

So far as the writer was informed, it has not been definitely determined whether the causative agent is a microscopically visible organism, a filtrable virus, or a toxin. Therefore, it seems right throughout the course of the studies to try to keep entirely open-minded, to be not overly influenced by superficial appearance of analogy with any other disease, to consider constantly the possibility that in this epidemic of encephalitis we were dealing with a disease or a type of disease different from any other which previously had prevailed in this country or, perhaps, in any other country, to collect facts carefully and thoroughly, and to consider every possible factor which might operate in the causation and spread of this disease.

The geographic distribution of the epidemic appeared to furnish a lead. There must have been some definite difference between the communities which were heavily affected and those which were lightly affected or not affected at all. The determination of these differences and whether they were consistent seemed highly important. In the areas heavily affected, the disease appeared to attack in about the same proportion rich and poor, white and Negro, and persons of different national descents. Difference in sources of water supplies for drinking and culinary purposes in two or more adjacent areas did not appear to affect the prevalence of the disease. Difference in food habits did not appear to affect prevalence. No evidence was found of a disproportionately high prevalence of the disease among users of milk, ice cream, or any other food from any one source. Therefore, it seems that if either water supplies or food supplies had operated in the spread of the disease all of the supplies in the large areas affected would have to have been about equally involved.

The first 2 days of these studies (September 18 and 19) were spent by the writer in the St. Louis region for conference and observation with other officers engaged in intensive studies in that region. We made repeated trips back

and forth over the St. Louis City line through different parts of the then heavily affected, thickly built-up suburban zone in St. Louis County.

As the city line was crossed going into the suburban zone, one difference was striking and very apparent. In the city area there were both sewage and sewerage. In the suburban area there was sewage but no adequate sewerage. In the city the sewage is carried away by trunk sewers to the disposal plants and eventually to the river. In the suburban zone, which is a section of hills and dales, there is no general sewerage system and the sewage from the small municipalities and from the thousands of dwellings and places of business is carried by small municipal sewers or by private or individual sewers direct from toilets or from cesspools or septic tanks to nearby creeks or streams. These heavily polluted open streams are very offensive to sight and smell. Even if they had nothing to do with the causation or spread of any disease, they are bad. They should not be tolerated in any community.

Since the rainfall in this region in the summer of 1933 was less than that for any of many previous summers, sewage was concentrated to an unusual degree in these creeks in the summer and early fall of this year. Mosquitoes, mainly (or almost solely) *Culex pipiens*, were breeding in myriads in these heavily sewage-polluted creeks. The citizens generally in these areas stated that mosquitoes were much more numerous and much more of a pest this season than they had been for many years before. Surgeon L. L. Williams, Jr., stated that *C. pipiens* and *Culex quinquefasciatus* mosquitoes bred under such conditions are capable of and addicted to long flights—2 miles or more. Anyhow, in September of this year, *C. pipiens* mosquitoes were observed from time to time in rooms in some of the farthest downtown leading hotels of St. Louis. The probability is that they were present more or less in all parts of the city, but most abundant in the outlying western areas.

Mosquito breeding in open sewage-polluted creeks was kept in mind in the course of the observations in other communities. East St. Louis is located in a flat, river bottom area instead of in one of hills and dales, and there was comparatively little, if any, mosquito breeding in exposed heavily sewage-polluted streams or other waters. Collinsville, Ill., however, is located in an area of hills and dales—very similar to that of the St. Louis County zone—and there was observed on each of the two sides of the village a heavily sewage-polluted creek in which in September mosquitoes (*C. quinquefasciatus*, mainly) were breeding in myriads. In the Independence and Blue Township region between Independence and Kansas City creeks were heavily sewage-polluted and *C. pipiens* were breeding therein to a much greater degree apparently than in the St. Louis County region as a whole. Columbia, Mo., presented this condition to a considerable degree. Kansas City, Jefferson City, Sedalia, and Chicago appeared free from it. Louisville, Ky., presented it to a marked degree in the immediate vicinity of each of the two areas in which encephalitis was highly prevalent.

Thus, throughout the limited observations made by the writer, the abundance of sewage-bred mosquitoes (*C. pipiens* or *C. quinquefasciatus*) appeared to be the only consistent factor of difference between communities which were heavily affected by encephalitis in this epidemic and those which were not affected or only slightly affected.

This one fact is not conclusive but it is suggestive and, therefore, seems worthy of careful consideration and further study. It is possible, of course, that some other insect, such as the sandfly or buffalo gnat (Simuliidae), or some unusual large fly or one not yet even thought of is the vector; but the evidence obtained in the course of these studies points to the mosquito as the most likely conveyor—if the disease is conveyed by insects. Every fact observed in the places visited by the writer seems in line with the hypothesis of mosquito conveyance and not one fact observed is in conflict with it. Thus, hypothesis passes into theory.

The geographic distribution and most other general features of the epidemic appear definitely out of line with the other much discussed hypothesis—and the one yet favored by some of the observers—that the disease is caused by an infection discharged in the secretions from the upper respiratory passages of patients and "carriers" and is transmitted

from person to person through direct and indirect personal contact. In the outbreak of malignant smallpox in Kansas City and vicinity in 1921 and in the influenza epidemic of 1918, the epidemiological pictures were very different from that of this encephalitis epidemic.

In view of the fact that only one person in about a thousand in the St. Louis region developed encephalitis in the course of the epidemic, negative results from human experimentation evidently would have to be produced on a large scale—involving hundreds of persons—to tend to nullify the mosquito conveyance hypothesis or any other reasonable hypothesis.

In considering the hypothesis that encephalitis is caused by a micro-organism, a virus, or a toxin conveyed to susceptible persons by mosquitoes, a number of interesting questions arise, such as the following:

1. Do the mosquitoes before becoming capable of conveying the causative agent have to feed on the blood of a person ill with the disease, or of one harboring the causative agent without being ill, and carry the agent through a developmental cycle as is the case with yellow fever and malaria?

2. May adult mosquitoes become capable of conveying the causative agent mechanically—as appears to be the case with some of the insects which convey the infections of some of the trypanosomiases—after feeding on the blood or some of the secretions or excretions of a person (ill with the disease or before, after, or without illness) harboring the causative agent?

3. May mosquitoes while in the larval stage acquire the causative agent in their feeding on matter polluted with human excretions or secretions or on other matter and continue to harbor the agent and be capable after reaching adult life of conveying the agent to persons by biting or otherwise?

4. If mosquitoes become loaded with the agent before leaving their breeding places (as appears to be the case with the mites which convey the infection of tsutsugamushi fever) is it one out of many—thousands or millions—or a considerable proportion of them which becomes loaded?

5. Is the causative agent harbored by the loaded mosquitoes for a period of days or weeks or for only a few hours after leaving their breeding places?

6. Is one loaded mosquito capable of conveying the causative agent to a susceptible person by one bite or are a number of bites by one or many loaded mosquitoes required?

7. Do other animals—such as poultry, birds, cows, horses, squirrels, rodents, or even fish or reptiles (dead or alive)—serve as sources of the causative agent from which mosquitoes may transmit the agent to man?

8. Are persons who "do not mind" mosquitoes, and who sit out in the open after dusk of evening and "take them," more likely to contract encephalitis than are persons who are "poisoned" by mosquitoes and who try to get away from them?

9. Is it possible that the part of the body bitten is a determining factor, as is the case with rabies virus, tending to explain why elderly persons with well-clad bodies and whose faces and necks present the main field of attack for mosquitoes are more likely under comparable conditions of exposure to loaded mosquitoes to have the causative agent conveyed effectively to them than are lightly clad young persons whose legs and arms present the main area of attack?

10. Are persons with foul mouths and offensive breaths or with otitis more likely while sleeping under cover at night to attract *C. pipiens* mosquitoes to their heads and necks than are persons with clean mouths sleeping in the same rooms or houses?

Most of these questions, presumably, will have to be answered, if at all, by the findings from future studies; but if in the meanwhile the spread of encephalitis is not proved to be due to some agent or agency other than mosquitoes, these questions are and will be serious practical ones.

The sudden spread of the disease over large areas, the very unusual occurrence of more than one case in one family, and the other general features of the epidemic seem to suggest that if the causative agent is conveyed by mosquitoes, it is conveyed by filth-breeding and filth-liking mosquitoes (*C. pipiens*) which, in rare exception or in considerable proportion, come "loaded" from some of their breeding places and are capable for a short time of conveying

the causative agent without previously having fed on the blood of a person or other living animal.

Incidence in Institutions

Institutions, of which there are quite a number in the outskirts and suburbs of St. Louis City, seemed to furnish especially strategic situations for studies of encephalitis. Four institutions were visited. The first one, an institution for mental cases administered by Sisters of Charity, had a population, including personnel and inmates, of about 400. It is located on a hill about 2 miles from Clayton in St. Louis County and in a zone in which encephalitis was highly prevalent. All parts of the building were found to be well screened and otherwise in excellent hygienic condition. Not a case of encephalitis developed at that institution during the epidemic.

On a hill in one of the outskirts of the city in the vicinity of a section of the St. Louis County zone which was quite heavily affected are three city institutions, the Hospital for the Insane, the Isolation Hospital, and the Infirmary (Almshouse). They face north on the same street and are in adjacent grounds. The Isolation Hospital is in the middle. The prevailing winds are from the south. All three are supplied with milk, meat, vegetables, and other foods purchased by the city from the same contractors. All three obtain their water supplies from the same source, the city public supply.

At the time of the survey, on September 25, the Isolation Hospital and the Hospital for the Insane were found to be well screened and otherwise in excellent structural condition, but the Infirmary was found to be poorly screened and in some parts in need of structural repair. Doctors, nurses, and other persons in each of these institutions were queried regarding mosquitoes in wards and other sleeping quarters at night. The report for the Isolation Hospital and the Hospital for the Insane was that very rarely was a mosquito noticed in the sleeping quarters, but the report for the Infirmary was that mosquitoes were abundant and very troublesome in the sleeping quarters. At the Isolation Hospital, in which over 300 cases of encephalitis had been treated during the epidemic, not a case had occurred among the personnel. At the Hospital for the Insane with a population, including personnel and inmates, of about 4,000, not a case had occurred.

At the Infirmary, with a population, including personnel and inmates, of about 1,200, 13 cases of encephalitis had developed during the epidemic. Two of these were in female attendants who were domiciled with six other female attendants in a large ward on the second floor of the south side of the building. The first case was in an attendant who slept in a bed directly in front of the door leading from an open porch into the ward. The screen on this door had sagged and furnished little protection against mosquito invasion. The second case, developing 6 or 7 days after the first, was in an attendant whose bed was at the same end of the ward and located a few feet toward the wall from that of the attendant who developed the first case. The other six attendants who were domiciled in this ward and who were not stricken with the disease slept in beds located at the other end of the ward in the part of the quarters farthest away from the door. The space of about 40 feet between the set of 2 beds and the set of 6 beds was used as a lounge.

At both the Hospital for the Insane and the Infirmary, contact through visitors and otherwise with the outside world was free during the epidemic; but, for obvious reasons, there was more restriction at the Hospital for the Insane than at the Infirmary with respect to permitting inmates to visit homes in the community and go out into and sit around in the institutional grounds after sundown.

Intensive Studies in the Independence Region

The encephalitis studies in the region of Independence were begun on September 19 and were terminated on September 28. They comprised (*a*) a survey of sanitary and other general conditions in the community, (*b*) examination of the morbidity and mortality records of the health office of Independence City and of the Jackson County Health Department, (*c*) a search for mosquito breeding places in the vicinity, (*d*) visits to homes and collection of detailed epidemiological histories

of 19 cases of encephalitis among residents of Independence City and of 28 cases among residents of Blue Township in Jackson County.

Independence is the seat of government of Jackson County. It is an attractive little city with rolling topography, wide, clean streets and well-kept homes, and without serious overcrowding in any part. Economic conditions generally appear considerably above average for cities of its size. The land area is about 3 square miles and the population in 1930 was 15,296, 14,450 whites and 846 Negroes (U. S. Census). Of the whites, only 488 are foreign-born.

Independence is located east of the northeast section of Kansas City, the distance by road between the limits of the two cities being about 6 miles. The public water supply, furnishing over 90 percent of water used for drinking and culinary purposes in the city, is obtained from the Kansas City supply. The milk supplies and other dairy products distributed in the city are from Kansas City and from local dairies and nearby dairy farms. About 50 percent is said to be pasteurized and most of the remainder to be grade A raw. Practically all meats sold in the city are distributed by Kansas City dealers. Vegetables are mainly from Kansas City markets and nearby farms.

About 80 percent of the private dwellings and public places are connected with the city sewers and the remainder are provided with septic tanks, cesspools, or privies. The main trunk sewer, carrying about two-thirds of the city's sewage, discharges into Rock Creek, a shallow stream ranging in width from 3 to 10 feet, meandering in and out along the southern outskirts of the city, and finally discharging into a lake in Mount Washington Cemetery about 1 mile from the eastern limit of Kansas City. The sewage before discharge into the creek (in the south central outskirts of the city) goes through some sort of sedimentation treatment which evidently is inadequate because the sewage was found highly putrescible after it entered the creek. Samples of water dipped from Rock Creek and from other heavily sewage-polluted creeks in the other outskirts or suburbs of the city were found, on September 22, to be literally teeming with mosquito larvae, which on examination proved to be *C. pipiens*. The locally prevailing winds are from the south.

Local Prevalence of Encephalitis

Independence was severely affected by the encephalitis epidemic. From August 19 to October 21, 1933, 63 cases with 14 deaths were reported among the residents of the city. Sixty cases were in white persons and 3 were in Negroes. The case incidence for the whole period of the epidemic in Independence was 1 to about 250 of population.

Blue Township in Jackson County, especially that part lying between Independence and Kansas City, was also severely affected. In that intercity zone the case incidence was 1 to about 125 of population, The population of Jackson County, exclusive of Independence and Kansas City is 55,406. Of them, 27,356 reside in Blue Township outside Independence. In this total rural population of Blue Township there were reported from August 19 to October 14, 1933, 61 cases of encephalitis with 8 deaths, a case incidence of 1 to about 450 of population.

In the total population of 28,056 in the other rural townships of Jackson County not a case was reported within that period. All cases

Table 2. Distribution of cases of encephalitis lethargica in Independence and Blue Township, Mo., by age and sex, 1933

Age (years)	Independence			Blue Township			Total
	Male	Female	Total	Male	Female	Total	
0–4	0	0	0	0	0	0	0
5–9	0	0	0	3	0	3	3
10–14	2	0	2	4	1	5	7
15–19	1	1	2	1	1	2	4
20–24	0	0	0	0	2	2	2
25–29	5	2	7	1	2	3	10
30–34	0	1	1	4	3	7	8
35–39	3	2	5	5	4	9	14
40–44	0	2	2	1	4	5	7
45–49	0	4	4	1	0	1	5
50–54	3	2	5	2	3	5	10
55–59	5	2	7	1	1	2	9
60–64	0	1	1	1	1	2	3
65–69	5	2	7	1	2	3	10
70–74	2	2	4	0	1	1	5
75–79	0	0	0	3	4	7	7
80–84	3	2	5	0	1	1	6
85–89	1	0	1	0	0	0	1
Total	30	23	53	28	30	58	111

Table 3. Incidence of encephalitis lethargica in Independence, Mo., by age and sex, 1933

Age (years)	Population			Cases	Incidence of cases to persons
	Total	Male	Female		
Under 5	1,170	607	563	0	0–1,170
5–9	1,367	726	641	0	0–1,367
10–14	1,326	636	690	2	1–663
15–19	1,308	656	652	2	1–654
20–24	1,533	736	797	0	1–1,533
25–29	1,339	635	704	7	1–191
30–34	1,061	503	558	1	1–1,061
35–44	2,045	962	1,083	7	1–292
45–54	1,728	824	904	9	1–192
55–64	1,256	611	645	8	1–157
65–74	768	346	422	11	1–69
75 and over	388	194	194	6	1–64
Unknown	7	4	3	5	----------
Total	15,296	7,440	7,856	58	1–264

reported in Blue Township outside Independence were in white persons. In the rural part of the township, only 60 Negroes reside. The area of Blue Township west of Independence, which probably was more heavily stricken by the epidemic than any other area of considerable population, is hilly. In the dales between the hills are numerous creeks. Most of these creeks are polluted with sewage and are heavily polluted in periods of drought such as that of the summer of 1933. Samples of water dipped from a number of places in those creeks on September 22 were found to contain myriads of *C. pipiens* larvae. The report from the residents generally was that mosquitoes were much more abundant in July, August, and September of this year than in the corresponding months of any previous year within their recollection. The opportunity for the breeding of mosquitoes in heavily sewage-polluted water in this region, in proportion to population, seemed several times as great as that furnished in the St. Louis County region.

The zone between Independence and Kansas City is quite thickly built up, resembling for the most part a scattering village. The majority of the residents appear to be in good or fair economic circumstances. Most of the water used for drinking and culinary purposes in this zone is piped from the Kansas City supply. The large majority of the homes seem well constructed and well kept. It was surprising to find among the streets at the front of some of the rows of those attractive homes gutters filled with and flowing with highly offensive sewage.

Dates of Onset of Cases

In a large majority of the cases especially investigated, the onset of definite illness was sudden or after a prodromal period of only a day or two. The dates of onset (usually those upon which the patient took to bed) of 51 cases in Independence and of 59 cases in Blue Township (outside Independence), whose histories on this point were obtained, were evenly distributed throughout August and September. [Tabulation omitted.—EDITOR.]

Age and Sex

The occurrence of cases of encephalitis among 111 persons in different age-sex groups is shown in table 2. It is interesting to note that in persons under 15 years of age the case incidence was much higher among males than among females.

The case incidence among persons in different age groups among 15,296 residents of Independence is shown in table 3.

Table 4 presents the number of persons in the different age groups in the rural farm and the rural nonfarm population of Jackson County, the number of cases of encephalitis in each of

Table 4. Incidence of encephalitis lethargica in Jackson County, Mo., by age and population group, 1933

Age (years)	Population		Number of cases	Relative but not actual case incidence
	Rural farm	Rural nonfarm		
Under 5	1,292	4,042	0	0–4,042
5–9	1,559	4,384	3	1–1,461
10–14	1,645	3,706	5	1–741
15–19	1,415	3,177	2	1–1,588
20–24	1,042	3,017	2	1–1,508
25–29	917	3,396	3	1–1,132
30–34	1,006	3,322	7	1–474
35–44	2,215	5,724	13	1–440
45–54	1,971	3,696	5	1–739
55–64	1,450	2,524	4	1–631
65–74	918	1,697	4	1–424
75 and over	326	923	8	1–115
Unknown	22	22	5	----------
Total	15,778	39,630	61	1–640

the age groups, and, since the large majority of the cases were in the nonfarm residents, the case incidence based on the nonfarm groups of the population.

Findings at Affected Homes

In the course of epidemiological studies, the ascertainment of definite information as to the possibly salient conditions to which the persons affected with encephalitis have been exposed prior to illness is of primary and fundamental importance. Therefore, visits to the homes of persons in which cases of encephalitis had developed in the Independence region were begun with interest and with an effort toward complete openmindedness.

Of the affected homes, 18 in the city and 27 in the township (outside Independence) were visited. At the second home visited, a history was obtained that within the 3 weeks prior to the onset of the patient's illness, 25 of about 100 chickens kept in the yard had died of some sort of convulsive disease. At the fourth and fifth homes, a history was obtained that within several weeks prior to the development of each case, goldfish kept in a bowl in the house or in a rock garden in the yard had been dying. At the seventh home visited, the wife had captured three strange insects in the bedroom of her husband the day he became ill with encephalitis. These insects, resembling somewhat the drones of honey bees, were later identified at the St. Louis headquarters of the studies as moths of unusual occurrence in that part of the world. The convulsive chickens, the sick goldfish, and the strange moth tales, however, did not continue, no history of any of them being obtained at any of the other stricken homes visited.

Especial consideration was given to the possibility of the encephalitis epidemic having been caused by a toxin—comparable to that of botulism—conveyed in some widely distributed canned or otherwise prepared food, but the histories of the cases definitely eliminated such etiological possibility. Attention also was given to the possibility of unhealed wounds, sores, bad tonsils, and diseased gums serving as a nidus of infection. The proportion of cases among persons with diseased gums was found to be quite interesting.

Possible Susceptibility Factors. No evidence was obtained to suggest that hay fever, asthma, hives, herpes, previous attack of any infectious disease, vaccination against smallpox, or immunization against diphtheria or typhoid fever tended to make one especially susceptible to the disease.

Of the 47 cases of encephalitis intensively studied in the Independence region, only 4 were in persons who gave a history of frequent colds or sore throat prior to onset of the illness, only 6 were in persons who had bad tonsils, 3 were in persons who were subject to fever blisters, 12 were in persons who during the 2 weeks or more prior to illness had unhealed wounds or sores, and 24 were in persons who had diseased gums and/or badly decayed teeth. Definite histories of mouth conditions were obtained for 18 city cases and 22 township cases. The 18 city cases were in persons who during the 2 weeks or more prior to their onsets of encephalitis had mouth conditions as follows: 10 with Riggs' disease, 2 with Vincent's angina severely affecting the gums, 4 with false teeth, and only 2 with healthy gums and sound natural teeth. The 22 township cases were in persons who during the 2 weeks or more prior to their onsets of encephalitis had mouth conditions as follows: 12 with Riggs' disease, 2 with false teeth, and 8 with healthy gums and sound natural teeth. In a sufficient proportion of instances to be somewhat impressive, the one member of a family who had a foul mouth was the one member who developed encephalitis.

Water and Foods

There was no evidence that any water supply used for drinking operated as a factor in the spread of encephalitis. The distribution of cases among users of the different water supplies was in close proportion to the numbers in the general population exposed to the different supplies.

No evidence was obtained pointing to milk or any milk product as a factor in the spread of the disease. The number of cases among the users of milk from the different milk supplies of the community was as nearly proportionate to the amount of the milk distributed by the different dealers as could be expected with such a limited number of cases. There

was no disproportionately large number of cases among consumers of milk or any other dairy product from any one source. The heavier milk drinkers and ice cream consumers of the affected families generally escaped the disease. A large majority of the cases were in persons who used milk sparingly (in coffee or on cereals) or not at all.

No evidence was obtained to suggest that meat, vegetables, or fruit, or any other food supplies were a considerable factor in the spread of the disease. Only 5 of 18 cases in the Independence group and only 4 of the 24 cases in the Blue Township group—whose histories on this point were obtained—were in persons who, within the 3 weeks prior to onset of illness, ate any food or drank any beverage of an unusual nature either at or away from home to which other members of their families were not also exposed. The incidence of the disease appeared less among beer drinkers than among nonbeer drinkers in the community, and there was no suggestively large proportion of cases among those who habitually drank beer of any one particular brand.

Sanitary and Hygienic Conditions. The large majority of the encephalitis cases were in persons residing in dwellings with apparently good sanitary and hygienic conditions, excepting that with respect to exposed sewage in the street gutters and nearby creeks.

Animals on Premises. The presence of animals at the 18 affected homes visited in the city and in 27 affected homes visited in the township was determined.

Unusual Insects. In 18 of the affected city homes visited, large gray flies of an unusual kind were reported to have been present in large numbers at 4 and small black flies at 2. In 27 of the affected township homes visited, large black flies of an unusual kind were reported to have been present at 1, bottle flies (in large numbers) at 1, and small black flies at 1.

Personal Contact. Among the 122 homes in which cases were reported in the encephalitis epidemic in the Independence region there were only two instances of more than one case in a home. Two cases occurred in one of the homes in the city and two in one of the homes in Blue Township. The interval between the onsets of the two cases in the city homes was 25 days and that between the onsets of the two cases in the township home was 7 days. The affected households in the zone averaged 4.5 persons. Therefore, the total number of persons who did not develop the disease in those 122 households was about 425. The case incidence in the Independence region was 1 to about 200 of population. In view of these data, it seems that residence in a home with a case of encephalitis did not increase the risk of contracting the disease.

Of the 47 cases specially studied, only 3 gave a history of direct association and only 1 of indirect association (through another member of the family) with previous cases of encephalitis, and among these 3 are included the 2 cases developing in previously affected households. Thus, it appears that if personal contact operated as a considerable factor in the spread of the disease, it must have done so in a very quiet, mysterious, and obscure manner.

The persons not developing the disease in the stricken households of the Independence region were, according to the histories obtained, remarkably free during the period of the epidemic from ailments of a sort to suggest the possibility of a mild case of encephalitis. In only 2 of the 45 households visited were histories obtained of such ailments in other members of the household. In one a son of the patient suffered with a "cold" during the 2 weeks prior to onset of the encephalitis case, and in the other the wife of the patient had an "intestinal upset" for 2 days about 1 week before the development of the encephalitis case.

Two instances were discovered of the occurrence of more than one case of encephalitis among persons at place of occupation—one at a public school in the city, where a librarian and a janitor had their onsets of illness 5 days apart, and the other at a printing office in the city, where the cashier had her onset of illness on August 22, and her successor at the desk, on August 29, 6 days after going on the job.

Biting Insects. Of the encephalitis cases especially studied, 19 city cases and 28 township cases, 9 had a history of having been bitten by insects other than mosquitoes 2 or 3 weeks prior tc the onset of illness. In the city, 4 persons

had been bitten by small black flies or gnats and 1 by large black flies. In the township, 2 persons had been bitten by fleas, 1 by large black flies, and 1 by small black flies.

Every one of the persons who developed the disease gave a definite history of having been bitten by mosquitoes frequently and many times during the period of 3 or 4 weeks immediately prior to, and extending to a time within a few hours of, onset of illness. Thus, mosquitoes appeared to be the only biting insect to serve as the epidemiological common denominator to all the cases.

At each of the homes visited, the one member of the family who "did not mind" mosquitoes and who was not "poisoned" by them was the one who developed the case of encephalitis.

Discussion

The observations and reports on the encephalitis epidemic in Missouri in 1933 indicate that the flight of mosquitoes in the regions in which the disease was highly prevalent began to diminish about September 15, and by the end of that month was probably less than 10 percent of that of the period of maximum flight. Following a heavy rain and a pronounced drop in temperature in the night of September 26, both the flight and the larval life of mosquitoes suddenly decreased very much in the Independence region. Twenty-five dippings on September 28 from places in Rock Creek and in other polluted creeks in the vicinity showed only two live larvae. Every dipperful of water from those same places on September 22 had shown scores or hundreds of live larvae. Thus, it appears that the epidemic in each of the most heavily affected regions began and reached its height when and where mosquitoes (*C. pipiens*) were unusually and tremendously prevalent, decreased as the mosquito flight decreased, and ceased to prevail (in epidemic rate) when adult mosquitoes in the vicinity became scarce or ceased to travel. Such coincidences are significant.

The epidemic in Missouri this year seemed to present many epidemiological features similar to those of the epidemic in the Inland Sea region of Japan in the summer of 1924. Mosquitoes found in the vicinity of Osaka have been identified as *C. quinquefasciatus* and/or *C. pipiens* (*2*). It would be interesting to ascertain whether they were unusually abundant in the Inland Sea region in the summer of 1924.

Conclusions

1. The preponderance of epidemiological evidence supports the hypothesis that encephalitis lethargica of the epidemic type which prevailed in Missouri and neighboring States in the summer and autumn of 1933 is caused by an agent (micro-organism, virus, or toxin) which is conveyed to persons by mosquitoes (*C. pipiens* and/or *C. quinquefasciatus*) which have bred under some set of unusual conditions in waters heavily polluted with human sewage, thereby becoming capable for a short period—perhaps only a few hours—of conveying the causative agent to persons by biting or otherwise without previously having fed upon the blood of a person or other living animal harboring the causative agent.

2. The installation of sewerage systems and other appropriate measures should be carried out as promptly and as thoroughly as may be practicable, before the summer of 1934, in every city, town, village, and suburban and other thickly settled community to prevent the breeding of *C. pipiens* and/or *C. quinquefasciatus* mosquitoes in surface streams, creeks, rivers, ponds, lakes, or other exposed collections of water which are or which are likely to become heavily polluted with human sewage.

3. From all the evidence obtained in the course of these studies, it appears improbable that water used for drinking and culinary purposes, milk or other foods, insects other than mosquitoes, or personal contact, either separately or together operated as very considerable factors in the spread of the disease.

4. Persons generally, and especially those over 50 years of age, in communities in which encephalitis prevails or is likely to prevail in epidemic rate should hasten to secure needed corrective work to put their gums and teeth in hygienic condition.

5. Encephalitis lethargica should be made a reportable disease by Federal, State, and local health agencies.

6. Studies of the cause and mode of spread of encephalitis should be continued unceasingly and adequately until complete practical knowledge of the subject becomes available.

REFERENCES

(*1*) Leake, J. P.: Encephalitis in St. Louis. J. A. M. A. 101: 928–929, Sept. 16, 1933.

(*2*) Howard, L. O., Dyar, H. G., and Knab, F.: The mosquitoes of North and Central America and the West Indies. Washington, D. C., Carnegie Institution of Washington, 1915, vol. 3, pt. 1, pp. 345–382.

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EDITOR'S NOTE: *The theory of mosquito transmission of encephalitis, detailed in the foregoing paper, was touched upon briefly in a paper read by Dr. Lumsden at the 29th annual meeting of the Southern Medical Association in St. Louis, Mo., in November 1935 and published in the March 1936 issue of the Southern Medical Association Journal, vol. 29, pp. 303–308.*

Air Pollution

Wagner College. The sixth annual symposium on air pollution and its control will be held at Wagner College, Staten Island, N. Y., on Saturday, April 26, from 9 a. m. to 4 p. m.

Participating in the symposium will be air pollution control officials from government and industry, and specialists in the fields of engineering agriculture and public health.

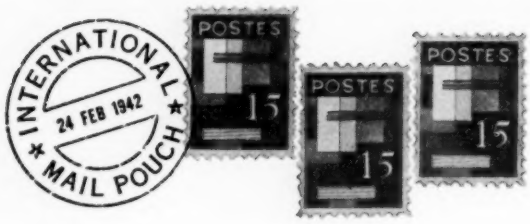
This year's program will emphasize the legal, technical, and legislative aspects of interstate air pollution control, and the contribution of industry to the abatement of atmospheric contamination.

The symposium is sponsored by Wagner's department of bacteriology and public health. Dr. Natale Colosi, chairman of the department, is in charge of the symposium.

University of North Carolina. Concentration of course work in air pollution, offered in fulfillment of the master's degree, has been announced by the School of Public Health of the University of North Carolina, Chapel Hill. Courses are open to sanitary scientists and sanitary engineers.

The department of sanitary engineering, which has a grant from the Community Air Pollution Program of the Public Health Service, will direct the studies.

University of Minnesota. Specialized graduate courses in air pollution will be offered in the spring quarter of 1958. This summer, from August 4–15, a workshop in air pollution will be open to qualified physicians, engineers, chemists, and other sanitation personnel. Inquiries should be addressed to Dr. Gaylord W. Anderson, Director, School of Public Health, College of Medical Sciences, University of Minnesota, Minneapolis 14.



Tax Victory

The health center in Concepción, Paraguay, won a victory when the municipality dropped its building tax on latrines. The levy of 250 guaranies equaled the total construction cost of the latrine, and made the price prohibitive to many families.

—M. A. TAFF, JR., *chief, health, welfare and housing field party, U. S. Operations Mission, Paraguay.*

Second Try

The paramount chief, two clan chiefs, district commission members, and the director of public health nursing spoke at the first graduation of a class of four unlettered midwives in Gbarnga, Liberia. Only the three midwives who failed to pass did not enjoy the festive occasion. Two of them remain undaunted, however, and are enrolled in the next class of 10 pupils. Recruiting for the midwives course goes on in all important clan areas. Classes are scheduled for 8 different locations, including the Gbarnga clinic.

—E. L. MASTHOFF, M.D., *medical officer, U. S. Operations Mission, Liberia.*

Pilgrims and Smallpox

After pilgrims returning from Kerbella, Iraq, introduced 21 smallpox infections in Iran, Iranian and Iraqi public health officers of the provinces along the common border met to develop a control plan. Dr. Franz Rosa, U. S. Operations Mission, Iran, visited Iraq for 5 days to help work out a joint and coordinated plan of action by the two countries to combat the disease.

Opportunities for the introduction of smallpox into Iran by Kerbella pilgrims resulted from several factors. Some travelers were not vaccinated as they left or reentered Iran. Nor were they immunized in Kerbella, where the disease has not been effectively controlled. Police and quarantine authorities overlooked vaccinating or examining infants, who were regarded as "baggage."

Infected ailing pilgrims were carried all the way across the country on buses; some were not even identified when they crossed through quarantine posts. Ineffective vaccination, illegal border crossings, false vaccination certificates, concealment of infected travelers, and failure to check certificates or to isolate cases also contributed to transmission of the virus.

Vaccination and quarantine measures have since been strengthened. Now only 10 percent of the pilgrims leaving the country are unvaccinated as they reach the border. Previously, a third of those returning from Iraq, having left Iran several months earlier, were not vaccinated. Every unvaccinated person that is seen at the border station is being immunized.

—GLEN W. MCDONALD, M.D., M.P.H., *chief, Public Health Division, U. S. Operations Mission, Iran.*

Thai Promoter

The headman of Bang Tao, Thailand, is the strongest advocate of the privy program. After a trip to Bangkok he came back determined to promote in his own village the progress he'd seen in other parts of the country. As a result, enthusiastic participants in Bang Tao's health project have bought 300 privy slabs.

The villagers at first objected to the privies on the religious principle which forbids more than one human fecal deposit in the same place. Now installing a privy is the popular thing to do in Bang Tao. Slabs are sold at cost and the money put into a revolving fund to make additional slabs. Health department sanitarians assist in selecting sites and installing slabs.

Interest in health education and community organization ran as high in the 7 villages of Tambol Gatoo, our first demonstration area. Villagers as well as community health council members joined in the self-help project. Privy slabs have been selling almost as fast as they are produced; 500 have been installed.

Other phases of this project include protection of private and public water supplies, premise sanitation, and improvement of preventive and medical care facilities of the local health centers.

—ANDREW P. HAYNAL, *deputy chief, public health adviser, U. S. Operations Mission, Thailand.*

Oklahoma's Heart Disease Course for Multidisciplines

KIRK T. MOSLEY, M.D.

SCIENCE teaching has the responsibility of keeping workers in the field abreast of new developments. This task of communicating information to those responsible for translating scientific advances into health services for individuals, families, and communities is often complicated by the fact that this information cuts across many disciplines. Public health especially embraces a variety of services demanding broad understanding by many individuals working together to accomplish their purposes.

These people must be made to feel more competent in their own fields and to know how their services complement the services of workers in other disciplines.

Accordingly, a course on heart disease was offered at the University of Oklahoma, May 28–June 9, 1956, with the basic purpose of providing better services to heart disease patients through increasing the knowledge and skills of workers in various disciplines. The course was designed to show the importance of and give opportunities for a team approach by those with the various skills and technical abilities required to take care of the needs of the patients.

Representatives from voluntary and official agencies at local, State, and national levels participated in the planning meeting. National bodies represented were the American Heart Association, the National League for Nursing, and the Public Health Service. On the State level those represented were the Oklahoma State Heart Association, Oklahoma League for Nursing, the Oklahoma State Health Department, and the School of Medicine, the School of Nursing, and the Extension Division of the University of Oklahoma. These State agencies subsequently became the co-sponsors of the course. Planning committee members included nurses, social workers, nutritionists, physicians, and educators.

The course of instruction, scheduled for 2 weeks, was offered by the department of preventive medicine and public health of the School of Medicine, through the Extension Division of the University of Oklahoma. Qualified students successfully completing the course received 2 hours of university credit.

Enrollment was limited to 30 with a special effort being made to enroll students representing a variety of disciplines. A total of 27 students attended all or part of the course. In this group were 8 physicians (health officers); 11 nurses, 5 of them from official health agencies, 4 from hospitals, 1 a private duty nurse, and 1 from a heart clinic; 4 dietitians; 1 nutritionist; and 3 social workers. Attendance at some sessions, counting resource persons from contributing agencies, rose to 50.

The faculty was provided by the School of Medicine and the School of Nursing of the University of Oklahoma, the Oklahoma State Health Department, the American Heart Association, the Oklahoma State Heart Association, and the Public Health Service.

The Oklahoma State Heart Association and the Oklahoma Department of Health each sponsored 15 tuition scholarships, and the lat-

Dr. Mosley is chairman of the department of preventive medicine and public health, School of Medicine, University of Oklahoma, Oklahoma City.

ter in addition paid for the maintenance of all department employees who attended. Secretarial help was provided by the heart association, the university, and the health department. Literature, films, slides, and mimeographed materials were provided by the heart association and health department. Classroom and other visual aid equipment was supplied by the medical school.

Instruction was offered in a variety of ways with emphasis placed on student participation and teamwork. Field visits, special conferences, and clinics occupied the morning sessions. After lunch the entire class assembled to hear lectures on subjects dealing with the physiology of the circulatory system, etiological factors and preventive aspects of heart diseases, and recent advances in research on the cardiac disorders. Following the lectures, students met in small groups for discussion and exchange of information about the field experiences in which they participated during the morning period. At a seminar session held the last hour of the day, students had an opportunity to discuss with a panel of appropriate experts a selected phase of the heart disease program.

Field Experience

For the field experience, one of the most successful aspects of the program, the class was divided into 5 small groups, each with students from 2 or 3 disciplines. Each member of a group was assigned a different type field activity each day, and no two members of the same group participated in the same activity together. For example, during a morning period, one member of a group might be assigned to observe bedside nursing care of a cardiac patient in a hospital, another member to accompany a public health nurse on a home nursing visit to a cardiac patient, a third member to visit the vocational rehabilitation office for a conference on the role of this agency in the rehabilitation of cardiac patients, and a fourth member to visit the food clinic and confer on diets for cardiac patients.

This arrangement provided the group with varied experiences and encouraged the exchange of information between group members.

Among the institutions and facilities visited as a part of the field experience were the Oklahoma Medical Research Foundation, Oklahoma State Heart Association, Department of Public Welfare, State Industrial Commission, physical medicine department of the Oklahoma School of Medicine, Crippled Children's Commission, a nursing home, cardiac catheterization clinic, medical wards, social service and dietetics departments of the University Hospitals, cardiac conferences for children and for adults, heart station where electrocardiographic examinations are made, rheumatic fever clinic, and a convalescent hospital. During the visit students were given an opportunity through discussion and conference to obtain a better understanding about the role of the agency or facility in providing services to heart patients.

"Handout" Materials and Tests

Three portfolios, Social Service Information, Nursing Information, and Nutritional Information, were distributed to each member of the class. Each of the portfolios contained 8 to 10 pieces of literature which had been obtained from the Public Health Service, heart association, or other sources. In addition to the literature, a carefully selected bibliography which included visual aid material was distributed. Thus, each student could take home from the course the most recent literature available for the various disciplines.

Tests before and after the course were given to gauge student progress. These tests comprised hypothetical family situations based on case material from the University Hospitals and health department files. The individual responses uniformly indicated an increasing knowledge about heart diseases and the problem of patients with heart diseases. The answers also revealed an increased awareness of the need to coordinate the services of professional workers responsible for the care of cardiac patients. The results of the tests reflected definite achievement toward the chief objective of the course, better care for the heart patient.

Followup Conferences

Approximately a year after the course, about 14 persons met with one of the instructors from

the Public Health Service for a followup conference. Through this group approach an attempt was made to get tangible evidence of the value of the course expressed in terms of better patient care. The remainder of the class were contacted by letter. These are some of the experiences reported:

• A nursing supervisor, who participated as a resource person, reported she had had a feeling of frustration after the course because she had been made aware that nurses in the hospital were not "nursing the patient." She is now director of the Baptist School of Nursing in Oklahoma City.

• A private duty nurse, who for 1½ years had been caring for a patient with cirrhosis of the liver, said she understood better how to give her patient, a physician, a low sodium diet. The nurse prior to going on duty with her current patient had for 2 years taken care of cardiovascular disease patients only.

• A hospital dietitian, who is now an instructor in a school of nursing, reported that she had prepared teaching materials centered on the patient with cardiovascular disease rather than on the diet.

• One medical social worker, serving on a national committee, felt she was more helpful in selecting teaching materials for schools of social work. She had been active also in establishing communication between the new medical social worker in the school of medicine and those in other disciplines.

• One of the health officers said that during the course he had learned for the first time that State health department nutritionists were interested in the problems of special diets for the cardiovascular disease patient and had begun using their services. Recently, he became the assistant to the director of the division of local health services in the Oklahoma Department of Health and now is serving as consultant throughout the State.

In Tulsa a different approach was used. The supervising nurse had shared her course of instruction with the nurses in the district to which she was assigned. These staff nurses reported their experiences to the group. One nurse asked a private physician regarding dietary problems of the patient for whom the physician had requested nursing service in giving a diuretic. At first the physician rejected the idea; later he acknowledged the visiting nurse's contribution by requesting visits to other patients. Nurses in other supervisory districts felt that they too would have benefited by instruction from the supervisor who attended the course session.

This followup evaluation added much to the significance of the course and provided useful information in planning future courses of instruction.

How to Set Up a Heart Course

For schools wishing to offer a heart disease course for multidisciplines similar to the one at the University of Oklahoma, the Heart Disease Control Program of the Public Health Service has prepared the following outline describing step by step the development of the course. This outline may serve as a checklist; however, it is only suggestive since individual situations cannot be anticipated, and its chronology cannot possibly be more than relative.

ASSUMPTIONS

That the course will be held at an established university or college for a minimum period of 2 weeks.

That an approximate number hours of credit in the school will be given, if desired, to those who are eligible.

That a properly representative committee will take the leadership in effecting the course.

That the whole-hearted cooperation of all the necessary participant agencies will be attained.

That the need for, and interest in, the course will have been determined in advance.

That all of the requisite resources, both human and material, are available and can be fully utilized.

PRELIMINARY PHASE

Appoint a "heart course" steering committee.

Establish overall objectives.

Select a course coordinator.

Choose nonconflicting dates.

Nominate faculty members and verify their acceptance.

Assign responsibility for media publicity.

See that participating agencies are personally briefed.

Determine number and disciplines of students.

Arrange for classrooms, housing, meals, and transportation, as necessary.

Determine the financing of the course: tuition and registration fees, selective scholarships, and so forth.

INTERMEDIATE PHASE

Determine course content, teaching methods, and format.

Explore clinical facilities available for field experience and observation.

Arrange for selected patients to be observed.

Prepare and mail announcement brochures to predetermined list of prospective students.

Choose and obtain visual aids and equipment.

Check availability of library facilities for reading assignments.

Assemble family and patient summaries from live case material selected from agencies sending students.

Appoint a qualified writer to prepare proceedings of the course for subsequent publication.

Arrange for secretarial and other such assistance.

Prepare detailed schedule of classes, conferences, and observations which permits flexibility in meeting individual needs.

FINAL PHASE

Prepare bibliographies, and select "hand out" literature.

Prepare sheet of suggested problem areas for group work.

Provide guide questions for observations.

Prepare pretests and posttests, based on point 7 in "Intermediate Phase."

Prepare a course "opinionnaire" for students.

Supply applicants with advance reading assignments as desired.

COURSE BEGINNING

Register students and distribute necessary instructional materials.

Divide class into teams, each to include various disciplines.

Permit each team to select a problem to study.

Provide each team with a full-time counsellor, or consultant.

Give students pretest.

Obtain from students written statements of individual objectives in the course.

Follow up on media publicity.

Throughout course allow for group decisions and flexibility indicated by student reactions.

COURSE ENDING

Give posttest.

Distribute "opinionnaire" for completion.

POSTCOURSE

Arrange for on-the-job followup of students to identify tangible results from the course.

Reassemble group for followup evaluation conference if possible.

Make resultant improvements in subsequent courses.

Some Epidemiological Aspects of Cervical Cancer

RAYMOND F. KAISER, M.D., and ALEXANDER G. GILLIAM, M.D.

EPIDEMIOLOGY is concerned with study of disease in human populations. In common with other medical sciences, its objective is to determine the factors related to or governing disease occurrence. Unlike other medical sciences, however, its universe of study is the human population or segments of it. Through observations of human experience it attempts to determine the characteristics of those people who develop disease, and of those who escape it. This, in turn, involves the measurement of risk to disease in groups of people with different characteristics.

Epidemiological methods of measuring risk to cancer, and other presumably noninfectious processes, have for the most part been borrowed directly from techniques of proved usefulness in communicable disease study. To a large extent these techniques have been dependent upon the stage of development of other disciplines of medical science. For example, it required relatively simple observations in human experience prior to the birth of the science of bacteriology to demonstrate beyond reasonable doubt that diphtheria was communicable. An understanding of important aspects of its natural history, however, had to await the development of simple and inexpensive laboratory tests which would detect those persons infected but not sick and would evaluate the relative immunity status of the population.

In cancer, observations in human experience were directly responsible for the beginning of what has developed into an enormous amount and variety of experimental research. The first experimental cancers were produced by painting tar on rabbits' ears, an undertaking prompted by the observation in humans that risk to cancer of the scrotum appeared to be excessive in chimney sweeps. Until the development of the Papanicolaou vaginal cytology test (*1*, *2*), however, laboratory research had provided no tools for the epidemiologist to use in extending our present relatively crude descriptive epidemiology of cancer. While it is true that cervical biopsies were introduced as long ago as 1878 by Ruge and Veit (*3*), it is, to say the least, impracticable to attempt cervical biopsies on large numbers of apparently well women. Though the Papanicolaou test does not satisfy all of the requirements desired by the epidemiologist, it is the first simple, acceptable laboratory test which can be applied to large numbers of well women and will select for further diagnostic evaluation most of those with cervical cancer.

Before this test could be used effectively in general epidemiological studies, a number of questions had to be answered. Could it be effectively applied in general population groups of apparently well women? What were its limits of specificity and sensitivity in such groups? What were the practical logistical problems?

Dr. Kaiser and Dr. Gilliam are both with the National Cancer Institute, Public Health Service, serving as chief and assistant chief, respectively, of the Field Investigations and Demonstrations Branch.

What was the cost in money, equipment, and personnel? Although some of these and other questions have been answered with regard to use of the test as a diagnostic adjunct in clinic and office practice, the only answer to its practicality in general epidemiological study, or as a cancer control measure, lay in an attempt to use it on a communitywide basis. Recognition of this fact led to such a study in Memphis and Shelby County, Tenn. The study was instituted in July 1952 as a joint endeavor of the University of Tennessee, the National Cancer Institute of the Public Health Service, and a host of other individuals and agencies.

Many important facts have already emerged from this study (*4*). Sufficient preliminary data are now available for examining other facets. It is the intent of this presentation to provide a brief background of the disease itself and some descriptive facts and apparent facts of the epidemiology of cervical cancer.

The Disease Itself

Carcinomas of the uterus may be classed in three groups: epidermoid, or squamous cell, carcinoma of the cervix, endometrial adenocarcinoma of the corpus, and adenocarcinoma of the cervix (*5*). Epidermoid carcinoma of the cervix and adenocarcinoma of the corpus appear to be quite distinct entities in histological structure, clinical behavior, and selective factors associated with their occurrence. Adenocarcinomas of the cervix are less clearly differentiated from the other two groups because of the difficulty in determining the precise point of origin of some adenocarcinomas of the lower part of the uterus.

The relative frequency of the 3 types of uterine carcinoma varies considerably from one reported series of cases to another, but broadly speaking cervical carcinoma is 3 or 4 times as common as endometrial, and cervical epidermoid carcinoma is at least 10 times as common as cervical adenocarcinoma (*5*).

At least some, and conceivably a large part, of the differences in relative frequencies of fundal and cervical carcinoma, as reported in different series of cases, is due to the different composition of each series with respect to age, race, marital status, and other selective factors associated with the occurrence of the two diseases. Most published series do not provide the data on such characteristics, which are necessary to make adequate appraisal of the large differences in recorded relative frequency.

Most epidermoid carcinomas of the cervix arise directly from the stratified epithelium of the external os or the portio vaginalis. Occasionally the origin may be from metaplastic stratified epithelium formed within the cervical canal or glands, or in an endocervical polyp (*5*). The development of the disease in the cervix is not dependent on the presence of the body of the uterus since it occurs after subtotal hysterectomy performed for other uterine disease. While occasional specimens of early cervical carcinoma afford evidence that the growth has arisen, not from a single minute focus, but from a considerable field of epithelium, no clear instances of genuine multicentric origin have been described (*5*).

In addition to frankly invasive malignant lesions of the cervix, histological lesions have been described since 1910 which fulfill all criteria of malignancy except invasion (*6*). As a result of his work with the colposcope, Hinselmann, as quoted by Traut and Benson (*7*), described in 1924 four classes of lesions of abnormal cervical epithelia from dysplasia through anaplasia, and intraepithelial cancer to invasive cancer. The term carcinoma-in-situ was applied to the most definitive of these patterns of abnormal epithelium in 1932 (*8*). Since then, this lesion has been variously labeled surface carcinoma, intraepithelial carcinoma, intramucosal cancer, and carcinoma-in-situ. It is now generally agreed that it may be preinvasive cervical cancer or an early stage of cervical carcinoma. However, there is considerable controversy as to the significance of other epithelial changes, such as dysplasia, hyperplasia, and anaplasia, and their possible relationship to invasive carcinoma.

Since 1932, much literature has appeared concerning the minimum histological criteria necessary for diagnosis of carcinoma-in-situ, as has data on its frequency, incidence, and its significance. Its relation to invasive cancer is inferred because of its histological appearance (*6*) and, according to Schottlaender and Kermauner, because of its occurrence at the pe-

riphery of infiltrating lesions (*9*). The relationship is also inferred because of its demonstrated presence prior to the development of some invasive cancers (*9–12*), and its detection at an earlier average age than usually observed for invasive cancers at this site (*4, 9*). The determination of the relationships of the carcinoma-in-situ lesion to classical cervical carcinoma is of paramount importance. To accomplish this, questions primarily epidemiological in nature must be answered.

Some of the more fundamental questions involved in this relationship are:

1. Do all invasive cervical cancers begin as intraepithelial lesions? If not, what percentage do?
2. Do intraepithelial lesions invariably progress to invasiveness? What percentage do?
3. What is the time required for an intraepithelial lesion to progress to invasiveness?
4. Do some intraepithelial lesions regress and disappear? How often does this occur?
5. Is it possible for an intraepithelial lesion to remain noninvasive indefinitely?
6. What are the age-specific incidence and prevalence rates of carcinoma-in-situ and invasive carcinoma? Are there race-specific variations in such rates?

Whether or not all invasive cancers of the cervix pass through the in-situ stage, and whether this intraepithelial lesion is reversible or always progresses to invasiveness, is not known at the present time. Its recognition, however, besides introducing problems regarding treatment (*13*), has opened new avenues for study of the essential pathogenesis of cervical cancer (*14*).

A large part of the attention now devoted to intraepithelial lesions of the cervix may be attributed to the extensive use of the cytological technique of Papanicolaou. By means of this test definitive diagnostic procedures may be directed to those women who are considered most likely to harbor invasive cancer (*4*). In addition, the test leads to the histological diagnosis of many intraepithelial lesions which otherwise would have remained undetected.

Clinically, the onset of carcinoma of the cervix is generally characterized by an absence of alarming symptoms. Those which would lead to its early discovery may give no concern to the patient during menstrual life. As a result, it frequently progresses into a moderately advanced disease before discovery, and early carcinomas of the cervix (stage I) make up only about 10 percent of the cases seen in many clinics (*15*). In addition, stage for stage, carcinoma of the cervix carries a much poorer prognosis than cancer of the body of the uterus.

The League of Nations' clinical classification of these cancers, adopted first in 1929 and modified in 1937 and in 1950, divides the disease into five stages. Stage 0 is reserved for carcinoma-in-situ and the remaining four stages are reserved for progressively extensive stages of the invasive disease. Patients treated in stage 0 should respond with uniform cure. According to Heyman (*15*), survivorship thereafter becomes progressively worse as treatment is instituted in advanced stages of the disease; there is about 60 percent recovery for stage I and 8 percent recovery for stage IV. Results from treatment in different clinics vary considerably, but factors responsible for such variation cannot be fully assessed. It is clearly evident, however, that the stage of disease at the time treatment starts is of paramount importance in cure. This fact emphasizes the necessity for obtaining a full understanding of the quantitative relationship of carcinoma-in-situ to invasive cancer of the cervix.

Extent of Uterine Cancer Problem

With the exception of the single year 1914, deaths in the United States attributed to cancer of the uterus were grouped with cancers of all female genital organs until 1930, when the fourth edition of the International List of Causes of Death came into use. Since then, uterine cancer deaths have been tabulated annually by age and race (*16, 17*). Analysis of these data shows a consistent decline in the age adjusted death rates for uterine cancer among white women since 1914 and among the nonwhite since 1930 (unpublished data, A.G.G.).

Death data for cancer of the cervix were first listed separately in 1939, but were not subdivided by age and race until 1949. Such data are of little practical value, however, in assessing the forces of mortality from cervical cancer, since such a high proportion of all

uterine cancer deaths are unspecified as to the portion of the uterus affected. In 1949, 43 percent and in 1955, 34 percent of all uterine cancer deaths were unspecified as to origin in the uterus. It is therefore not possible to determine whether or not cancer of the cervix and cancer of the corpus have participated equally in the decline in mortality attributed to cancer of the uterus as a whole.

During 1955, 15,170 deaths were attributed to cancer of the uterus in the United States (17). Among white women the crude death rate was 17.0 per 100,000 population. This rate was exceeded by only those for cancer of the breast (27.2 per 100,000) and cancer of the large intestine (17.5 per 100,000). Among nonwhite women more deaths were attributed to cancer of the uterus than to any other type of cancer, the crude death rate being 28.7 per 100,000 population. For both races combined, deaths from cancer of the uterus were exceeded by only cancer of the breast. According to unpublished data (A.G.G.), on the basis of rates for deaths from all causes recorded in 1955, 1.8 percent of white and 3.0 percent of nonwhite women would be expected to die eventually of cancer of the uterus.

Of those deaths for which the part of the uterus first affected was recorded on the death certificate, there were, in 1955, 17 times as many cervical as corpus cancer deaths among the nonwhite and 7 times more cervical cancers among the white. As pointed out, however, there was a substantial number of deaths among both races with unspecified origin of the disease in the uterus. In the unlikely event that all of those unspecified had arisen in the corpus, deaths due to cancers of the cervix would still predominate in both races, and the cervix-corpus ratio would still be greater in the nonwhite than in the white.

During this period of decline in mortality, the incidence of the disease has been increasing in at least one State. In New York, between 1942 and 1953, the cervical cancer incidence rate increased 7 percent, and cancer of the corpus, 21 percent (*18*). In Connecticut, on the other hand, the incidence of cervical cancer decreased 8 percent while corpus cancer increased 22 percent between 1935 and 1951 (*19*).

Based on reports from New York State, during 1949–1951, the lifetime probability of developing cervical cancer was 2.2 per 100 women, and cancer of the corpus, 1.5 per 100 women, or a total of 3.7 per 100 women for all uterine cancer (*20*).

Age Selection

The tendency of cancer of the cervix to occur earlier in life than cancer of the body of the uterus was well known at least as early as 1900. In Williams' series the maximum frequency was in the age group 35 to 45, as compared with the mode in the age group 50 to 60 for cancer of the corpus (*21*). While cases in persons under 20 years of age are uncommon, a few histologically diagnosed cases have been described in such persons (*22–24*), the youngest being an infant of 7 months with a cervical adenocarcinoma (*25*). In 1955, out of 8,804 deaths attributed to cancer of the cervix in the United States, 3 were under 5 years of age and 5 under 20.

Perhaps the most reliable data on age incidence of the disease are those from Denmark and Sweden. These data reflect the annual probability that women of various ages will develop or be diagnosed as having the disease. In Denmark, for the years 1942–44, the incidence rates for cancer of the cervix rose sharply from age 25 to a peak of about 70 per 100,000 in the age group 45–49, and declined fairly regularly thereafter (*26*). In Sweden a similar age selection is evident though the rates, age for age, are lower than observed in Denmark, and the peak of incidence occurs about 5 years later in life (*27*). The Swedish data also show a regular increase in incidence at all ages between the calendar years 1925 and 1945, an increase more marked than that observed in New York State.

In contrast with the type of age selection prevalent in Denmark and in Sweden, risk of the disease in Connecticut increases fairly regularly with age, and instead of declining after 45 or 50 continues to increase, reaching a peak in women 85 and over (*19*). A similar type of age curve is observed among white women in Shelby County, Tenn., but not among the nonwhite (*28*). In New York State the age selection is somewhat different from that observed

in either Denmark or Memphis (*20*). These regional differences in age selection are sufficiently great to warrant the suspicion that they are not artifacts, but no ready explanation is available for them. Further, in each locality, fairly distinct differences exist between the age selection of cancer of the cervix and of cancer of the body of the uterus. The consistently different age selection of cancer in the two parts of the uterus is one reason for suspecting that they represent two disease entities.

Race Selection

With the exception of limited morbidity data, and fairly extensive mortality figures for the white and nonwhite population of the United States, most of the evidence of racial selection of cervical cancer is derived from relative frequency data. Relative frequencies on some occasions faithfully reflect absolute variations in risk, but on other occasions they do not. In any case, there is probably no other type of cancer in which racial selectivity of the disease, as suggested by relative frequency evidence, offers such intriguing possibilities of better understanding its genesis.

On the basis of relative frequency figures, Williams claimed in 1900 that American Negresses were less prone to uterine cancer than white women (*21*). That the reverse is true is now amply demonstrated not only by mortality figures for a long period of time but by morbidity rates collected in special surveys (*28, 29*). Many doubt that the clearly excessive risk among the nonwhite women in the United States is due to actual racial susceptibility. Most workers contend that it is due instead to a number of factors which have been loosely classed as social or environmental (*30, 31*).

While the early relative frequency evidence for the white and the nonwhite women in the United States was not substantiated, evidence of a similar basic nature relating to Jewesses has been established as correctly portraying relative risk (*30*). There appears to be no longer any doubt that Jewesses experience substantially less risk to cancer of the cervix than the non-Jewish (*32, 33, 35*). A recent study in Israel has elicited very low incidence rates, and since Jewesses of different "ethnic typology" experience rates of about the same magnitude, the authors believe that it cannot be dependent on a racial factor, but is due instead to circumcision of Jewish males (*35*).

Except for absolute comparisons of risk relating to the white and the nonwhite population in the United States and Jewesses in Israel, most of the other evidence of racial selection involves relative frequency data. For example, Khanolkar's study relating to various classes of Indians attending the Tata Memorial Hospital in Bombay supports the idea that Hindu Decanni and Gujarti, and Moslem women, all experience a different risk to cancer of the cervix (*36*). Since, however, the evidence consists of relative frequencies, not incidence, it does not establish these differences.

Mortality statistics from different countries cannot be easily compared because of the different proportions of deaths in each country which are unspecified as to portion of uterus affected. For cancer of the uterus as a whole, however, the age adjusted death rate in 1950 in Japan was more than twice that recorded in England and Wales; about 40 percent greater than the rate among white American women; and about 40 percent less than that recorded among American nonwhite women (*37*).

Among the American Navajos, if relative frequency comparisons are accepted as evidence, risk of death from all uterine cancer would be twice that observed in American whites and about the same as noted in nonwhites as a whole. Adequate comparisons of absolute risk show, to the contrary however, that the risk for the Navajo is only half that observed for the whites and only a fourth of that noted for the nonwhites (*38*).

Geographic Distribution

Data on geographic distribution of cervical cancer consist of official mortality statistics, the results of summations of autopsy series, and morbidity surveys conducted in a few localities. While the data from only the latter are reliable as to the absolute probability of developing the disease, official mortality statistics and autopsy studies clearly show that cancer of the cervix has been recorded on every continent, in every large country, and among every important ra-

cial and ethnic group. Furthermore, the frequency of cancer of the cervix relative to all other cancer, as observed in the autopsy series, varies considerably from place to place. Whether or not risk of the disease varies in the same fashion cannot be determined from most such studies.

Within some countries for which pertinent data are available, incidence of the disease varies considerably. In Denmark the highest rates are observed in Copenhagen, and the lowest among the rural population (*39*). This excess risk among urban women also appears to exist in the State of Iowa (*40*). White women in southern cities of the United States appear to experience greater risk than do the northern white women (*29*), and in Copenhagen (*41*) and Pittsburgh (*42*) there is considerable variation in rates within the city. In these latter cities the higher rates are found in the poorer sections.

Marital and Pregnancy Status

The first clear evidence that cancer of the uterus and cancer of the breast tend to have an opposite selectivity with respect to marital status was presented apparently by Rigoni Stern in 1842. While only 6 percent of the uterine cancer deaths recorded in Verona, 1769 to 1839, were in unmarried women, 29 percent of the breast cancer patients were unmarried (*43*). These differences are the more striking in view of the fact that cancer of the uterus generally occurs at an earlier age when the probability of marriage is less than in later life. These data did not permit the firm conclusion that uterine cancer is more likely to occur among married women than among single, but they did demonstrate the striking difference from breast cancer in terms of selectivity according to marital status.

It has now been established that the annual probability of developing cancer of the cervix is greater in married than in single women (*39*, *44–46*). It would further appear that early age at marriage and instability of marriage are also associated with this disease (*47*, *48*). In addition, there is some reason for believing that other variables associated with instability of marriage are also associated with cancer of the cervix. Thus, there is scattered evidence that illegitimate births (*48*), syphilis (*49*), early sexual relations, multiple sexual partners (*31*), and prostitution (*50*) are all associated with this disease. On the opposite side of the coin, cervical cancer appears to occur very rarely among nuns (*51*).

Another variable associated with marriage, which has been given much consideration, is circumcision of the marital partner. This was due first to the observation that cancer of the cervix is less frequent among Jews, where circumcision is universal. Other races which practice circumcision at varying ages and to a different extent are alleged to have varying risk of cervical cancer. The so-called incidence reported for such races, however, is invariably a relative frequency which may or may not reflect relative risk to this cancer. Reliable data on the incidence of cervical cancer are very badly needed among such groups as the Moslems, Hindus, Bantus, and Fijis. Such rates can now be reliably and relatively inexpensively ascertained through discriminative use of the vaginal cytological technique.

Another variable which has long been associated with cervical cancer is pregnancy. Lane-Claypon's (*52*) data indicated an association between pregnancy, but not number of pregnancies, and cancer of the cervix. Maliphant's series (*44*) suggested the greatest risk in parous women, with each pregnancy adding slightly to the risk; the next greatest risk among childless married women; and a considerably reduced risk among single women. Logan's analysis of British mortality data suggested that marital status alone, apart from childbearing, seemed to be the factor associated with higher mortality (*45*). In Gilliam's series where a precise actuarial method was used in computing age specific pregnancy rates in several types of cancer patients, the difference in fertility between those with breast cancer and those with cervical cancer was limited to the first 30 years of life (*48*). After age 30, pregnancy rates in breast and cervical cancer patients were identical. A further curious finding in this series was the greater difference in pregnancy rates between the cervical cancer patients interviewed in 2 of the cities than was

observed between breast and cervical cancer patients in any 1 of the 3 localities.

It appears clear from the brief considerations mentioned that the role of these various factors associated with cervical cancer still remains to be clarified with additional and perhaps different kinds of systematically collected data.

Socioeconomic Status

It has been common experience of gynecologists that cancer of the cervix is less frequently encountered in private than in clinic practice. Mortality data for 1930–32 for Great Britain similarly indicated that risk of dying from uterine cancer as a whole increased with the decrease in socioeconomic status (*53*). That this is largely due to cancer of the cervix is now evident from analysis of similar death data for 1950 and 1951 (*46*). These show that when socioeconomic class is judged by occupations of husbands, the rates were lowest in women whose husbands were in the professional class and highest in wives of unskilled laborers, with a fairly regular gradient in the intermediate classes. Stocks concludes from these and other analyses of regional variation in mortality that the disease in Great Britain shows a relationship with overcrowded housing, social class distribution, and predominant industry 20 years before (*46*).

Infections and Cervical Lacerations

For a considerable period of time, chronic cervical infections and poor obstetrical care were believed to predispose a woman to carcinoma of the cervix. The idea that cervicitis or cervical lacerations might be the cause of this cancer is probably an outgrowth of the general theory of chronic irritation as the cause of all cancer. There appears to be little definitive evidence bearing directly on it one way or the other, however. From the histological standpoint, early cancers at this site are observed with no associated evidence of chronic irritation. Evidence of cervical lacerations, on the other hand, is common in parous women.

Gagnon is of the opinion that the rarity of the disease in nuns is due to the infrequency of cervicitis in this group (*51*). Cashman has noted that fewer cervical cancers than expected occurred in about 5,000 women who could be followed out of 10,000 women whose cervicitis had been treated by deep cauterization (*54*). If, however, there had been a very few cases among those women who were not followed, the results might have been quite different.

With regard to cervical lacerations, Lombard and Potter's case history study indicated an association between history of lacerations and this cancer (*47*). Gilliam's series, on the other hand, at least indicated no undue proportion of instrumental deliveries among cervical cancer patients (*48*). Since both studies depended upon histories as remembered by patients and controls, it is not certain that they correctly portray the actual facts. As for other evidence based on clinical impressions, there is still considerable difference of opinion among gynecologists as to the possible association of these factors and the disease. That even repeated trauma, and by inference cervicitis, is not necessarily involved is suggested by the apparent rarity of the disease in cases of prolapsed uterus (*55*).

Discussion

It should be clear from this brief account of some of the facts of distribution of cervical cancer among humans that many selective factors bearing on its occurrence have been recognized. There is a common, and perhaps unfortunate, tendency among students of cancer, however, to assign specific causal significance to such factors, often even before the facts themselves are well established. Thus, when it appears that cervical cancer is more common in parous than in nulliparous women, the statement soon after appears in texts, as though it were fact, that the disease is caused by cervical lacerations. When it is evident that Jewesses are less prone than the non-Jewish—then *ergo*, it is caused by intercourse with the uncircumcized. Or, when it appears there is a tendency to select women who marry early in life—it is caused by trauma of immature tissues. Or, when it is shown that risk is greater in syphilitics than in nonsyphilitics—it is caused by chronic irritation. Or, because it selects the lower rather than the higher economic classes,

it is caused by poor hygiene and inadequate general medical care.

All of these factors associated with cervical cancer may well eventually turn out to be causes. On the other hand, an equally tenable hypothesis at the present time is that the disease is caused by some presently unknown factor or patient attribute which is more commonly present in women with these characteristics, but is by no means limited to them. The fact remains that the disease does occur in virgins, in nullipara, in Jewesses, in the nonsyphilitic, and in women of the highest economic classes, to mention only a few of the selective factors. Demonstration of excessive risk in women with certain characteristics does justify a hypothesis. No useful purpose is served, however, by parading hypotheses as fact, a tendency all too commonly encountered among students of cancer in general.

Up to the present we are aware of no weaving together into a coherent and generally satisfying explanation of the disease the threads of facts regarding distribution of cervical cancer in humans. The development of the Papanicolaou test, however, provides a laboratory tool which, if properly exploited epidemiologically, can at least test and either dispose of or extend some hypotheses which have been paraded as fact.

REFERENCES

(1) Papanicolaou, G. N.: New cancer diagnosis. Proc. Third Race Conference, 1928, p. 528.

(2) Papanicolaou, G. N., and Traut, H. F.: Diagnosis of uterine cancer by the vaginal smear. New York, N. Y., the Commonwealth Fund, 1943.

(3) Novack, E.: Life and works of Robert Meyer. Am. J. Obst. & Gynec. 53: 53–64 (1947).

(4) Erickson, C. C., Everett, B. E., Jr., Graves, L. M., Kaiser, R. F., Malmgren, R. A., Rube, I., Schreier, P. C., Cutler, S. J., and Sprunt, D. H.: Population screening for uterine cancer by vaginal cytology. J. A. M. 162: 167–173 (1956).

(5) Willis, R. A.: Pathology of tumours. Ed. 2. London, Butterworth & Co., Ltd., 1953.

(6) Rubin, I. C.: The pathological diagnosis of incipient carcinoma of the uterus. Am. J. Obst. 62: 668–676 (1910).

(7) Traut, H. F., and Benson, R. C.: Cancer of the female genital tract. A monograph for the physician. New York, N. Y., American Cancer Society, 1954.

(8) Broders, A. C.: Carcinoma in situ contrasted with benign penetrating epithelium. J. A. M. A. 99: 1670–1674 (1932).

(9) Younge, P. A., Hertig, A. T., and Armstrong, D.: A study of 135 cases of carcinoma in situ of the cervix at the Free Hospital for Women. Am. J. Obst. & Gynec. 58: 867–895 (1949).

(10) Pemberton, F. A., and Smith, G. V. S.: The early diagnosis and prevention of carcinoma of the cervix. A clinical pathologic study of borderline cases treated at the Free Hospital for Women. Am. J. Obst. & Gynec. 17: 165–176 (1929).

(11) Petersen, O.: Precancerous changes of the cervical epithelium in relation to manifest cervical carcinoma. Clinical and histological aspects. Acta Radiol., supp. 127. Stockholm, 1955.

(12) Jones, H. W., Jr., Galvin, G. A., and TeLinde, R. W.: Intraepithelial carcinoma of the cervix and its clinical implications. Internat. Abstr. Surg. 92: 521–524 (1951).

(13) Taylor, H. C.: Controversial points in the treatment of carcinoma of the cervix. Cancer 5: 435–441 (1952).

(14) Dunn, J. E., Jr.: The relationship between carcinoma in situ and invasive cervical cancer. A consideration of the contributions to the problem to be made from general population data. Cancer 6: 873–886 (1953).

(15) Ackerman, L. V., and del Regato, J. A.: Cancer. Diagnosis, treatment and prognosis. Ed. 2. St. Louis, C. V. Mosby Co., 1954.

(16) U. S. Bureau of the Census: Mortality statistics, 1900–1936. Vital statistics of the United States, 1937–1944. Washington, D. C., U. S. Government Printing Office.

(17) U. S. National Office of Vital Statistics: Vital statistics of the United States, 1945–1955. Washington, D. C., U. S. Government Printing Office.

(18) Gerhardt, P. R., and Handy, V. H.: Trends in cancer incidence, mortality and probability in the State of New York. New York State J. Med. 57: 1387–1390, Apr. 15, 1957.

(19) Griswold, M. H., Wilder, C. S., Cutler, S. J., and Pollack, E. S.: Cancer in Connecticut, 1935–1951. Hartford, Connecticut State Department of Health, 1955.

(20) Randall, C. L., Gerhardt, P. R., Handy, V. H., and Kraus, A. S.: The probability of the occurrence of the more common types of gynecologic malignancy. Am. J. Obst. & Gynec. 68: 1378–1390 (1950).

(21) Williams, W. R.: Uterine tumours. Their pathology and treatment. New York, William Wood & Co., 1901.

(22) Scheffey, L. C., and Crawford, B. L.: Adenocarcinoma of the cervix in a 22-month-old child. Am. J. Obst. & Gynec. 24: 118–122 (1932).

(23) Speert, H.: Cervical carcinoma in young girls. Am. J. Obst. & Gynec. 54: 982–986 (1947).

(24) Heckel, G. P.: Carcinoma of the cervix in the first year of life. Pediatrics 5: 924–929 (1950).

(25) Baber, J. L., Rosser, E. ap. I., and Lavertine, J. D. O'D.: Carcinoma of the cervix uteri in an infant. Brit. M. J. 4703: 392–394, Feb. 24, 1951.

(26) Clemmesen, J., and Busk, T.: The age distribution of malignant diseases in Denmark, 1942–44. Acta Radiol. 30: 9–16 (1948).

(27) Lindell, A.: Carcinoma of the uterine cervix. Incidence and influence of age. A statistical study. Acta Radiol., supp. 92. Stockholm, 1952.

(28) Dunn, J. E., Jr., Rowan, J. C., Erickson, C. C., and Siegler, E. E.: Uterine cancer morbidity data: Memphis and Shelby County, Tenn., 1950–51. Pub. Health. Rep. 69: 269–274, March 1954.

(29) Dorn, H. F., and Cutler, S. J.: Morbidity from cancer in the United States. Part I. Public Health Monogr. No. 29. Public Health Service Pub. No. 418. Washington, D. C., U. S. Government Printing Office, 1955.

(30) Kennaway, E. L.: The racial and social incidence of cancer of the uterus. Brit. J. Cancer 2: 177–212 (1948).

(31) Wynder, E. L., Cornfield, J., Shroff, P. D., and Doraiswami, K. R.: A study of environmental factors in carcinoma of the cervix. Am. J. Obst. & Gynec. 68: 1016–1052 (1954).

(32) Versluys, J. J.: Cancer and occupation in the Netherlands. Brit. J. Cancer, 3: 161–186 (1949).

(33) Casper, J.: Incidence of uterine cancer among different ethnic groups. Schweiz. Ztschr. f. allg. Path. u. Bakt. 18: 764–774 (1955).

(34) Dorn, H.: Cancer morbidity surveys: A tool for testing theories of cancer etiology. Am. J. Pub. Health 45: 615–621 (1955).

(35) Hockman, A., Ratzkowski, E., and Schreiber, H.: Incidence of carcinoma of the cervix in Jewish women in Israel. Brit. J. Cancer 9: 358–364 (1955).

(36) Khanolkar, V. R.: Cancer in India. Acta Unio Internat. Contra Cancrum 6: 881–890 (1950).

(37) Segi, M.: Cancer mortality statistics in Japan, 1900-1954. Sendai, Japan, Department of Public Health, Faculty of Medicine, Tohoku University, 1955.

(38) Smith, R. L., Salsbury, C. G., and Gilliam, A. G.: Recorded and expected mortality among the Navajo, with special reference to cancer. J. Nat. Cancer Inst. 17: 77–89 (1956).

(39) Clemmesen, J.: On the etiology of some human cancers. J. Nat. Cancer Inst. 12: 1–21 (1951).

(40) Haenszel, W., Marcus, S. C., and Zimmerer, E. C.: Cancer morbidity in urban and rural Iowa. Pub. Health Monogr. No. 37, Public Health Service Pub. No. 462. Washington, D. C., U. S. Government Printing Office, 1956.

(41) Clemmesen, J., and Nielsen, A.: The social distribution of cancer in Copenhagen 1943–47. Brit. J. Cancer 5: 159–171 (1951).

(42) Patno, M. E.: Geographic study of cancer prevalence within an urban population. Pub. Health Rep. 69: 705–715, August 1954.

(43) Stern, R.: Fatti statistici relativi alle malattie cancerose. Giornali per Servire ai Progressi della Pathologia e della Terapeutica. Ser. 2, 2: 507–517 (1842).

(44) Maliphant, R. G.: The incidence of cancer of the uterine cervix. Brit. M. J. 4613: 978–982, June 4, 1949.

(45) Logan, W. P. D.: Marriage and childbearing in relation to cancer of the breast and uterus. Lancet 264: 1199–1202, Dec. 5, 1953.

(46) Stocks, P.: Cancer of the uterine cervix and social conditions. Brit. J. Cancer 9: 487–494 (1955).

(47) Lombard, H. L., and Potter, E. A.: Environmental factors in the etiology of cancer. Acta un. internat. contre le cancer 6: 1325–1333 (1950).

(48) Gilliam, A. G.: Fertility and cancer of the breast and of the uterine cervix. Comparisons between rates of pregnancy in women with cancer at these and others sites. J. Nat. Cancer Inst. 12: 287–304 (1951).

(49) Levin, M. L., Kress, L. C., and Goldstein, H.: Syphilis and cancer. New York State J. Med. 42: 1737–1744 (1942).

(50) Rojel, J.: The interrelation between uterine cancer and syphilis. Copenhagen, Nyt Nordisk Forlag. Arnold Busck, 1953.

(51) Gagnon, F.: Contribution to the study of the etiology and prevention of cancer of the cervix of the uterus. Am. J. Obst. & Gynec. 60: 516–522 (1950).

(52) Lane-Claypon, J. E.: Cancer of the uterus. A statistical inquiry into the results of treatment, being an analysis of the existing literature. Rep. on Health & Med. Subjects, No. 40. London, His Majesty's Stationery Office, 1927.

(53) Great Britain Registrar General: Decennial Supplement, England and Wales, 1931. Part IIA. Occupational Mortality. London, His Majesty's Stationery Office, 1938.

(54) Cashman, B. Z.: The prevention of cancer of the cervix. Am. J. Obst. & Gynec. 49: 190–196 (1945).

(55) Craver, L. F.: Etiology of cancer. J. A. M. A. 105: 1820–1824 (1935).

Animal Diseases and Human Health

On September 11–13, 1957, a Conference on Animal Diseases and Human Health was held in New York City under the joint auspices of the New York Academy of Sciences and the Public Health Service's Communicable Disease Center.

The significance of these diseases was discussed from two viewpoints: the direct transfer of disease by parasites or by consumption of diseased meat and milk, and the reduction of food supplies caused by outbreaks of animal disease.

Enzootic, epizootic, and zoonotic diseases were considered, along with means by which the diseases are transmitted. Some were examined because they present particular economic and public health threats; others because the study of animal diseases may enlighten students of human afflictions.

The conference discussions are represented here in summaries of 16 of the papers. The full proceedings are to be published by the New York Academy of Sciences.

Salmonellosis: Incidence and Control

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It is impossible to determine the incidence of salmonellosis in either man or animals. No systematic method of reporting salmonellosis of animals has been established, and one must rely on summaries of isolation and identification of causative agents dispersed throughout the medical and veterinary literature to estimate the frequency with which the bacteria occur among the lower animals.

Means of determining the incidence of the disease in man are practically in the same condition. Summaries published by the National Office of Vital Statistics are based on woefully inadequate reporting from a minority of States, and in most instances the etiological agents of foodborne infections are not accurately determined. Despite these deficiencies, one must rely upon these summaries for any estimate of the prevalence of *Salmonella* infections in the United States.

Despite methodological inadequacies with regard to incidence, the list of occurrences indicates that there is a direct correlation between salmonellosis of animals and man in any given locality, although the methods whereby the organisms are transmitted from animals to man and vice versa may vary from one region to another, depending upon sanitary facilities and habits of the population.

Numerous *Salmonella* serotypes have been isolated from animals used as food by man and from animals with which man comes into close contact. Not only have host-adapted types such as *Salmonella dublin* in cattle and *Salmonella choleraesuis* in swine been found frequently, but large numbers of types not adapted to specific hosts occur among domestic animals. While salmonellae are particularly numerous in swine, birds probably constitute the largest single reservoir in animals. The organisms have been isolated from turkeys, poultry, wild game, and egg products. Among the nonedible

animals and insects in man's environment, dogs, cats, rodents, flies, ticks, snakes, and tortoises have been incriminated as vectors of salmonellosis. Salmonellae have also been isolated from fish and shellfish, and the evidence indicates that these species encountered the organisms in water contaminated by man or other nonaquatic animals.

Since *Salmonella* types are widely distributed through the animal kingdom, there is small wonder that the organisms are frequently present in animal food products. Recent investigations have revealed their presence in an unexpectedly high percentage of meat and animal products, and this has resulted in a further investigation of the roles that food processing and human carriers have in salmonellosis. Carcasses in abattoirs have been shown to contain organisms more often than animals on farms, indicating that the abattoir environment and processing procedures favor the spread of the organisms. Investigators have also found salmonellae widely distributed in poultry-processing plants.

Although outbreaks in which human carriers were responsible for the contamination of meat products have been frequently described, the ultimate source is in no way certain since it might be said that the carrier state is an occupational hazard of those who continually handle uncooked meats and carcasses. Direct transmission may also occur from man to man without the intervention of food.

Means for control of the incidence and transmission of salmonellosis are slowly getting under way.

While there is a large reservoir of salmonellae in the lower animals, this situation can be expected to improve gradually. Tests for the detection of the infections and methods of eradication are being studied in fowl and cattle. Progress has been made in the eradication of salmonellae from poultry flocks through agglutination testing programs for *Salmonella typhimurium*. Possibilities of detecting *S. dublin* infection by agglutination tests have also been studied. Although the elimination of salmonellosis from flocks and herds cannot be accomplished in the immediate future, it is encouraging that animal pathologists are thinking of eradicating the infections rather than controlling them. It must be admitted, however, that this attitude is directed largely by economic considerations rather than by regard for public health.

In any effort to eradicate salmonellae from domestic animals it is necessary to take into consideration the continuous seeding of the population through infected feed, and such sources must be eliminated if *Salmonella* infections are to be eradicated from flocks and herds.

With regard to dissemination from person to person, every effort should be made to prevent the spread of organisms among the population by means of the excreta of patients, convalescents, and carriers. This is a joint responsibility of the practicing physician, the health officer, and the laboratory. Prompt isolation of patients with symptoms of intestinal infections and proper disinfection of the dejecta must be carried out until such time as a definite diagnosis is established. Contacts should be examined bacteriologically, and the strictest personal hygiene should be practiced in the household. Convalescents should be examined systematically until the bacteria no longer can be isolated from the excreta.

Stool cultures should be required from all food handlers, not only those in food dispensing establishments but those in food processing plants as well. In addition, hygienic conditions in these plants and establishments must be improved. It has been demonstrated that thorough and consistent cleansing of abattoirs and equipment results in a marked reduction in the recovery of salmonellae from carcasses and from the environment.

Researchers have suggested that bacteriological standards for the control of abattoir and food processing establishments would be helpful; that an approach similar to that employed in dairy products should be applied to other products of animal origin including fish and poultry; and that, in time, coliform organisms as an index to pollution may be successfully adopted for the bacteriological environment of meat processing plants as it has been adopted successfully in dairy products and shellfish.

Food technology has made giant strides within recent years, especially in the removal of food preparation from the family kitchen to

the large establishment. It seems in many instances that methods of control and measures for their enforcement have not kept pace with advances in food processing. More rigid control of products becomes even more important and practical when it is remembered that salmonellae may survive temperatures to which food products are sometimes subjected in cooking. Since it is possible to pasteurize certain food products effectively or to destroy salmonellae in them through a combination of acidification and mild heating, it would not seem unreasonable to adopt and enforce bacteriological standards for such products. New processes of food preparation and storage require new and improved procedures and practices to deal with them.

All of the writers who have given serious thought to the control of salmonellosis agree that effective control can result only through the cooperation of governmental agencies dealing with health, agriculture, and food. Further, it is agreed that salmonellosis should be a reportable disease of both man and animals, and that effective reporting and control measures should be enforced.

Through cooperation of physicians, health officers, veterinarians, and sanitarians with the proper governmental agencies, and through education of the public in the fundamental sanitary aspects of the preparation and preservation of foods, control of the infections may be expedited.

Newcastle Disease

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Newcastle disease is a minor occupational disease limited chiefly to persons working with chickens and eggs and to those concerned with control of the disease. The population at risk is rather sizable since poultry is raised on approximately 3,418,000 farms in the United States.

In all known instances, infection of man has been limited to the initial case, the transmission being from bird to man and never from man to man. Acute conjunctivitis is the usual manifestation, although systemic disease has been reported. Initial diagnosis of Newcastle disease in man is dependent mainly upon isolation of the virus, for the serology is complicated by certain problems of interpretation.

The importance of Newcastle disease lies in the resulting higher-priced poultry products and a reduction in their quality. The disease may kill, but more often it affects the poultry by interrupting growth and egg production, and it increases the percent of birds and eggs rejected for abnormalities.

While vaccination has permitted profitable production of poultry, it has not eliminated the virus in any part of the Nation, and it has not reduced the hazard of human infection. An organized control and eradication program is lacking, and without one the virus is afforded infinite opportunity to give rise to a mutant capable of maintaining itself in the human population.

Pulmonary Adenomatosis in Sheep

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Workers in various parts of the world have described several invariably fatal pulmonary diseases of sheep that can probably be grouped together into a complex of related entities.

Histologically, these diseases can be arranged in a spectrum, with pure infiltrative pneumonia or pulmonary lymphomatosis at one end, and metastasizing adenocarcinoma at the other. All degrees and combinations of inflammatory neoplastic disease occur between the two extremes, some forms being histologically indistinguishable from human pulmonary adenoma.

Representatives of all forms are naturally contagious, including the metastasizing adenocarcinoma of Peru, and there is considerable evidence that all forms in sheep are naturally transmissible. Experiments now under way with an infiltrative form occurring in Montana

indicate that transmission can be effected by inoculation of sheep with sterile centrifuged extracts of infected and frozen sheep lung. Although 1 to 3 years are usually required from the time of inoculation until symptoms appear, the disease develops progressively. Sheep sacrificed periodically after inoculation show pathological changes at least several months before symptoms are expected to appear.

Apparently pulmonary adenomatosis in sheep was entirely enzootic until early in the present century when epizootic disease appeared, inviting recognition of its contagious nature. Forms of pulmonary adenomatosis of similar histology and clinical course also occur in man. Whether etiological similarities obtain is an unanswered question at present. Information gained from the study of contagious animal neoplasm, however, may be useful as a guide to the future study of neoplasia in man.

Cat Scratch Disease

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The specific entity known as cat scratch disease, cat-bite fever, benign inoculation lymphoreticulosis, nonbacterial regional lymphadenitis, and so on, has been recognized as a common human disease only during the past decade. Actually, the condition was recognized as early as 1930 by Foshay in Cincinnati, Ohio, but published detailed descriptions did not appear until 1950.

Most cases of cat scratch disease follow scratches or bites by domestic cats. But other sources have also been recognized, including thorns, cat urine, and bone spicules. No definite clinical disease in the offending animals has been discovered.

Lymphadenopathy is the most characteristic lesion of cat scratch disease. Usually the nodes draining the area of the primary lesion are involved, but extension to other parts of the body may also occur. Thus the axillary and epitrochlear nodes are most commonly involved in scratches or bites on the hand and forearm, the inguinal nodes with lower limb lesions, and submandibular, suprascapular and cervical nodes following scratches about the face, neck, and chest.

In addition to the typical picture of regional lymphadenopathy, syndromes involving bone, central nervous system, eyes, and the spleen have been observed.

Geographically, the disease is widespread, having been reported in Europe, Great Britain, North and South America, and Asia. Undoubtedly many cases occur that are as yet unrecognized.

The causal agent has never been identified. It has been presumed that an agent similar to those of the psittacosis-lymphogranuloma venereum group is responsible, but recent information does not tend to confirm this presumption.

Extensive microbiological and pathological studies have been done and, although no proven etiological agent has been discovered, characteristic histological lesions have been described. There is no specific skin test that is quite accurate in diagnosis.

There are no public health methods presently applied for the control or treatment of this disease. As the association of man with domestic pets continues, increasing numbers of clinical cases are likely.

The Pan American Zoonoses Center

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The Pan American Zoonoses Center is an international institution dedicated to promoting and strengthening activities against the zoonoses in the Americas. Its services are available to health departments, agriculture departments, educational institutions, and other agencies interested in the zoonoses: those diseases naturally transmitted between animals and man.

The center, which has its central site in Azul, Province of Buenos Aires, Argentina, was established in August 1957. The Pan American Sanitary Bureau is the sponsoring international organization, although provisions have been made for other international agencies to

Main building of the Pan American Zoonoses Center in Azul, Province of Buenos Aires, Argentina. The only international institution of its kind, the center is primarily devoted to research on diseases communicated from animals to man. The center was established in August 1957 as a result of a special agreement the previous year between the government of Argentina and the Pan American Sanitary Bureau, Regional Office for the Americas of the World Health Organization.

join forces with the Bureau. Provisions have also been made for direct support of the center through contributions from any country.

The center is designed to educate and train professional and paraprofessional personnel in techniques and methods to combat the zoonoses. It will also (*a*) conduct research to improve diagnosis, epizootiological-epidemiological knowledge, and control procedures; (*b*) promote, aid, and coordinate such research in government and private institutions; (*c*) work toward the standardization of diagnostic methods for making and testing vaccines, serums, antigens, and other biological products; (*d*) prepare and disseminate information on the zoonotic diseases; and (*e*) develop field demonstration activities in accordance with the needs of participating countries.

Promoting and strengthening governmental activities against the zoonoses in the Americas is the principal function of the center. But this objective can be reached only insofar as there are sound technical activities and services in each country dedicated to research, control, and eradication of diseases common to man and animals.

While there are over 80 zoonoses, the center will give priority to those of major importance in the Americas: rabies, brucellosis, hydatidosis, tuberculosis, encephalitis, salmonellosis, psittacosis, and anthrax.

Leptospirosis in Man

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Human leptospiral infections comprise a multiplicity of separate syndromes whose clinical features vary from mild grippe-like illnesses to those simulating fulminant hepatitis or "aseptic meningitis." The classical disease, described by Weil in 1886, is caused by *Leptospira icterohemorrhagiae* and is recognized clinically by the development of fever, icterus, conjunctival injection, myalgia, hemorrhagic

tendency, renal, hepatic, and vascular failure, and a high fatality rate. Symptoms persist from 1 to 3 weeks. Leptospiremia and leptospirura occur at various stages and antibodies are demonstrable in convalescence.

The currently recognized human American species of *Leptospira* are *icterohemorrhagiae*, *canicola*, *pomona*, *bataviae*, and *autumnalis*.

Milder forms of illness result usually from infection by leptospirae other than *L. icterohemorrhagiae* and *L. bataviae*. Over 200 patients with leptospirosis contracted in a tropical environment had fevers enduring from 4 to 20 days, with an average of 8 days. Studies conducted in Malaya from 1954 to 1955 revealed leptospiral infections to be a significant cause of short-term pyrexia. Only two fatalities occurred among these patients and few presented overt clinical evidence of hepatic, renal, or cardiovascular insufficiency.

Clinical features may resemble aseptic meningitis. A leptospiral etiology should be considered in any illness characterized by fever, myalgia, nausea or vomiting, conjunctival injection, proteinuria and neutrophilia.

Rheumatoid Arthritis in Man and Arthritis in Swine

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Arthritis in swine is prevalent under farm conditions. In some cases, an infectious agent can be isolated; in others, none can be found. Pyogenic bacterial infections produce enlarged, soft joints distended with pus. This purulent type of infection occurs most frequently at the time of birth, probably through the umbilicus.

In *Erysipelothrix rhusiopathiae* infections, the organism may disappear from the joints while the arthritis persists. In such cases many macroscopic and microscopic pathological changes similar to rheumatoid arthritis in man are present.

In acute arthritis there is synovitis, characterized by vascular engorgement, and edema of the synovial tissues. The effusion is turbid or serosanguineous and mucinous. The synovial villi show evidences of beginning proliferation and beginning lymphocytic infiltration. Later, greater proliferation and less edema are observed. Proliferation of the mesothelial cells covering the hypertrophied synovial villi is present. The villi contain young, highly vascular connective tissue, plasma cells, and lymphocytes. A striking feature is the accumulation of dense collections of lymphoid cells resembling germinal centers of lymphoid tissue.

In advanced chronic arthritis with pannus formation of subchondral origin, fibrosis in the adjacent narrow spaces, increased vascularity, and collections of lymphocytes occur. Pannus formation over the articular cartilage with or without fibrous ankylosis, narrowing of the joint spaces with rarefaction of the adjacent bones, and greatly thickened capsules are evident.

A comparison of arthritis of swine and rheumatoid arthritis of man shows some similarities. In both diseases, the changes are essentially proliferative and nonsuppurative and have a tendency toward granulomatous proliferation in the synovial membrane. Pannus formation and focal accumulations of lymphocytes are observed. Destruction of cartilage at the site of pannus attachment and subchondral cellular reactions appear similar. Rarefaction of the bone as revealed by radiography and intra-articular fibrous adhesions are common to both diseases.

Listeriosis: A Public Health Problem

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Listeriosis is a little known, infrequently recognized, but widespread bacterial disease of man and other warm-blooded creatures. The causative agent, *Listeria monocytogenes*, has been recovered from man, mammals, and birds in a number of countries all over the world, and in 22 of the 48 States.

Morphologically, the organism is a gram positive, non-acid-fast, non-spore-forming rod.

There is a tendency for the organisms to arrange themselves into "V's" or into a palisade formation when the smear is made from solid media. The bacteria stain evenly and are 0.5 to 0.6 by 1.0 to 2.0 microns in size. Short, but sometimes long, threadlike chains may be observed in the rough phase of growth. Capsules are not demonstrable. Motility can be demonstrated in 6-hour glucose broth cultures, but it is more pronounced at 25° C. after 24 hours incubation. The peritrichously flagellated organisms have a characteristic tumbling motion.

Listeria frequently fails to grow when cultured from fresh tissues, but it has been found that refrigeration of the original necropsy specimens and periodic subculturing will increase the number of isolations obtained. There are four serotypes of *Listeria*, and among these are several biotypes. All serotypes and biotypes can and do attack man, poultry, and mammals.

The specificity of agglutinating titers is open to question since some serums spontaneously agglutinate antigen, and *Listeria* shares antigens with other bacteria. This being the case, agglutination titers should be interpreted with caution and preferably compared with the complement fixation test.

Listeriosis in sheep and cattle usually is readily recognized, and the etiological agent is frequently recovered without difficulty. The main clinical manifestations caused by *Listeria* in ruminants, swine, and man are meningoencephalitis, septicemia, and abortion. In animal infections, there is a definite seasonal distribution. The greatest number of animal cases occur during the winter and spring months. This does not appear to be true of human infections. Sex and age distribution in both animals and man appear to show little differences in the incidence of infection, but the younger the creature, the more unfavorable the prognosis.

Therapeutic agents have been evaluated in animals and man, and the tetracycline group have been found to be the most effective; penicillin and sulfonamides in combination proved almost as effective. The in vitro sensitivity gives some indication of the agent of choice. Vaccination of animals has been attempted, but the trials have not been wholly successful. Further tests, however, should be made.

Since 1950 there have been 83 human cases in the United States verified by the Communicable Disease Center's laboratories, and since 1954 there have been 2,106 animal cases (representing herd and individual cases). We may conclude, therefore, that listeriosis is a public health problem, especially since we do not know the frequency of occurrence nor do we understand the epidemiology of the disease. We do know that it is widespread, that it occurs in humans and animals, and that it is frequently fatal. We also know that the premature infant and the aborted fetus may be due to congenitally acquired *Listeria* which does not manifest itself in an overt illness of the mother, that all ages and both sexes are susceptible, and that animal contact is not necessarily a factor in the epidemiology of listeriosis.

Animal Disease and Biological Warfare

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Biological warfare may be defined as the intentional use of living micro-organisms or their toxic products for the purpose of reducing the military effectiveness of man. This use includes damage to or destruction of his food sources.

Do we have reason to concern ourselves with defense against such warfare? History answers in the affirmative. From the earliest to most modern times it tells us that nations at war will and have used every known weapon system that offers them a possibility of achieving victory.

What is the relationship of animal disease to defense against biological warfare? A brief exploration of three major facets of a biological warfare defense program reveals a close and vital relationship.

First is the field of potential antihuman agents. Would not the zoonoses, animal diseases transmissible to man, such as mycotic

infections, tularemia, and the viral encephalitides, to name but a few, dominate any such list? They certainly possess some of the characteristics considered in a good biological warfare agent such as high infectivity and stability.

Second is the field of antianimal agents. The widespread outbreak of such foreign animal diseases as foot-and-mouth disease, African swine fever, rinderpest, and Newcastle disease in our domestic animals, to mention but a few, could result in a drastic, if not complete, reduction of available food supplies. This would be particularly true if coupled with a successful destruction of crops.

Third, and perhaps the only silver lining in the defense picture, is the far-reaching benefits human health has received as a result of research in animal disease. Advances in epidemiology, bacteriology, and immunology, for example, are already actively utilized in advancing the health of the Nation.

Orphan Viruses of Man and Animal

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Refinement of tissue culture methods and expansion of their use into the field of virology has brought into focus large numbers of viruses heretofore unrecognized. It is well known that families of viruses, such as herpes and pox, exist in different species, and now it appears that there are also enteric viruses for a number of different animal species. These are enteric cytopathogenic orphan viruses for humans (ECHO), monkeys (ECMO), bovines (ECBO), and swine (ECSO).

ECHO viruses, of which there are at least 19 antigenic types, have been isolated from normal children and from patients with aseptic meningitis syndrome. Because the human diseases to which they belonged were unknown, and because they failed to produce illness in laboratory animals, including infant mice, they were originally called "orphan viruses."

The difference in colony (plaque) morphology and in host cell susceptibility have suggested that the ECHO viruses may be divided into two groups. The selection of the proper serum for antigenic identification has been made easier by such a preliminary grouping.

ECMO viruses are included among the simian viruses of Hull and his colleagues. They may be divided into three groups according to their plaque morphology and patas cell susceptibility. Positive CF reactions were obtained between strains of one group of ECMO viruses and human serum known to contain adenovirus antibodies.

ECBO viruses isolated by Kumin and by Klein grow readily in bovine kidney cultures; some have been found to propagate in monkey kidney cells, but not in HeLa cultures. Those tested have proved to be antigenically distinct from human viruses.

ECSO viruses were isolated from newborn pigs by Moscovici in Italy. The virus grew rapidly in monkey and swine kidney cells, but HeLa cells failed to respond.

In view of this study it is believed that colony morphology and cell susceptibility, classical criteria for classification of enteric bacteria, are of similar value for identification of orphan viruses isolated from man and animal.

Viral Hepatitis in Animals and Man

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Viral hepatitis has been described in man and other animals, including dogs, pigs, mice, and ducks. Such viral agents appear to be characteristically narrow in their host susceptibility. Since for laboratory investigations the viral hepatitis agents of man are not transmissible to other animal species and are difficult to evaluate in tissue culture, mouse hepatitis virus has been studied as a possible prototype of the human equivalent.

Mouse hepatitis virus in embryonated chicken eggs induces changes resembling the effect of acute serum from viral hepatitis of man. Inoculums containing virus induce an

increase in the number of lymphoid cells in the allantoic fluid; in inoculums containing heat-inactivated virus, the cellular response is absent. Serial passage of inoculated egg material has failed to show reproduction of murine and human hepatitis viruses in avian tissue. Four logs of mouse-infective virus are required to elicit the cytological response in embryonated eggs, thus indicating that the egg is very much less sensitive to virus than the natural host.

Mouse hepatitis virus does not propagate in "L" strain of mouse fibroblast in tissue cultures, and human hepatitis virus has induced no detectable cytopathogenic effect in cultures of human tissues.

A soluble complement-fixing antigen has been extracted from liver emulsions of mice infected with hepatitis. The antigen can withstand desiccation, heat, extraction with ether, and freezing; it does not sediment at 120,000 gravities for 2 hours. "Normal" liver does not contain this antigen. An antigenic relationship of mouse hepatitis virus to human disease has not been demonstrated.

Neutralizers of Human Viruses in Animal Serums

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Certain domestic animals, particularly cows, have neutralizing substances in their serums against certain human viruses such as polioviruses, coxsackie, and adenoviruses. These antibodies occur in the absence of any known infection with the agents and raise the question of their interpretation. Are they true antibodies?

A study of the neutralizing substance against polioviruses in cow serums revealed the following characteristics: It is a globulin, heat stable at 60° C. for 30 minutes and highly specific. Some serums have no neutralizing substances; others have neutralizing substances to types 1, 2, and 3 polioviruses or combinations of these. There is evidence of passive transfer: newborn calves commonly have neutralizing substances that disappear at 4 to 5 months and gradually reappear over a period of time in the traditional fashion of antibodies. Titers are variable and may be quite high: dilutions greater than 1:128 neutralize 100 TCD.

A review of the literature indicates that although certain nonspecific inhibitors may have one or more of these properties, no substance other than specific antibody is known to have all of these properties.

Even when one has determined that he is dealing with a true antibody, a more difficult question remains. What is the nature of the antigenic stimulus for the antibody? Cross reactions between viruses of which there are already many examples (canine distemper and measles, vaccinia and variola, swine influenza and influenza, psittacosis and lymphogranuloma venereum) make final interpretation or origin impossible.

The problem is particularly difficult in surveys of animal serums when one does not have the orienting information of a known reservoir, or an epidemic situation with a characteristic clinical picture and paired serums to observe a fourfold rise in titer.

Although one may conclude that the neutralizing substances in bovine serums are true antibodies that react with polioviruses, coxsackie, and adenoviruses, the final interpretation as to the origin of these antibodies requires the isolation of a specific agent that can explain the antibody pattern. In the absence of such isolations, the origin must remain an object of closely reasoned but inconclusive speculation.

Brucellosis in Livestock

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Brucellosis in livestock continues to be an important economic burden and public health threat in many sections of the United States.

Since 1934 a cooperative State-Federal program for the control and eradication of bovine brucellosis has been in operation. During that time the number of reactors disclosed through blood agglutination testing has declined from

11.5 to 1.8 percent of the animals checked. A similar reduction has occurred in the number of herds carrying the infection. For fiscal year 1935, infected animals were found in 36.2 percent of the blood-tested herds. As of June 30, 1957, this figure was 10.5 percent.

In October 1954 the bovine brucellosis eradication campaign was accelerated by additional Federal funds, and progress during the past 3 years exceeded that reported for any similar period since the program's inception. At present approximately half of all cattle in the United States are under supervision for the control and eradication of brucellosis.

The initial goal of the eradication campaign is to establish and maintain certified brucellosis-free areas. This designation signifies that the infection appears in no more than 1 percent of the animals and 5 percent of the herds. At the end of fiscal year 1957, 735 counties and 7 entire States were certified. Another 712 counties were actively working on programs leading to certification. This means that nearly 50 percent of all counties in the United States, Puerto Rico, and the Virgin Islands are either certified or are rapidly approaching that status. It is estimated that by June 30, 1958, a total of 16 States will be certified.

If the present level of field operations can be maintained, there is every reason to believe that the incidence of bovine brucellosis throughout the United States can be reduced to 1 percent or less by 1960.

Brucellosis in Man

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With more widespread pasteurization of milk and other dairy products, brucellosis in the United States has become almost entirely an occupational disease affecting persons intimately exposed to infected animals or their tissues. In the last 10 years the number of cases reported annually has dropped considerably; nevertheless, if one excepts salmonellosis deriving from animal sources, brucellosis in the United States still has a higher reported incidence than any other disease of animals transmitted to man.

While great strides have been made in the last few years in the control of bovine brucellosis, and the incidence of the infection in cattle has been greatly reduced, the decrease in notified incidence in man cannot be clearly related to the success of the control program. Swine continue to be an important source of infection for man.

Despite the decrease in the number of reported cases, the problem of establishing the diagnosis of the disease in man remains an important one. Isolation of the organism from the patient is the only proof of diagnosis. A significant titer in the standard seroagglutination test, or a rising titer, provides presumptive confirmation of a clinical diagnosis. In chronic brucellosis a fluctuating titer is suggestive of active disease. The widespread and often indiscriminate use of the broad-spectrum antibiotics makes cultural proof more difficult, and greater dependence must be placed upon the agglutination test. The skin test has no value as a diagnostic aid.

The current therapy of choice consists of a combination of dihydrostreptomycin and tetracycline, with or without the addition of sulfadiazine or triple sulfonamide. As all presently available drugs primarily suppress the infection, treatment must be continued for a period of time sufficient to allow the body to dispose of the infection. Bed rest is essential. Local lesions may require longer medical treatment or definitive surgical treatment.

Vector Relationships of Arthropod-borne Encephalitides in North America

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Although much remains to be learned about the ecology of the arthropod-borne encephalitides in North America, past and recent studies

have provided a considerable knowledge of these diseases. The most probable hosts and vectors have been revealed.

Field investigations have shown fresh water swamps to be the foci of eastern equine encephalitis (EEE) infection. Wild birds captured in swamps have frequently been found infected, and numerous virus isolations have been made from *Culiseta melanura*, a swamp-inhabiting mosquito which feeds principally upon birds.

Because of its restricted habitat and feeding preferences, *C. melanura* is probably unimportant in the direct epidemic spread of EEE to horses and man. Although it appears to play the important role of maintaining the virus in its endemic foci, the spread of the disease outside of these foci is most likely dependent upon other mosquito species which feed commonly upon horses and man.

Certain conditions appear necessary to permit an epizootic in horses (and an epidemic in man) to occur. Bird infection within the swamp foci would need to be at high level, furnishing a relatively great source of virus for mosquito infection. This condition would depend upon an adequate population of *C. melanura* (and perhaps other susceptible bird-feeding, swamp-inhabiting species), and a low immunity rate in the bird population. The latter would, in turn, depend upon a light infection rate the previous year. With a large number of birds infected, inevitably some of them fan out into adjacent nonswamp areas and serve as sources of infection for other mosquito species which will feed upon horses and man. The scattered distribution of the infected birds, together with a lack of strong bird-feeding proclivity on the part of the mosquitoes, results in only a very low mosquito infection rate; this must be compensated for by large mosquito numbers. If, in addition to all this, there is also a low immunity rate in the horse population, conditions are proper for an epizootic. Once the epizootic is under way, some transmission from horse to horse by mosquitoes and biting flies without the intervention of birds is probably also possible.

The ecology of western equine encephalitis (WEE) has undergone intensive investigation over many years. Serologic and virus isolation studies in wild birds have firmly established their role as the most important hosts, and hundreds of isolations of the virus from *Culex tarsalis* attest to the close association of this mosquito species with natural sources of infection. Since it is widespread in distribution, occurs in large numbers, feeds freely upon man and horses as well as birds, is exceptionally susceptible to infection, and transmits with high efficiency, it fulfills requirements for both an endemic and epidemic vector. It undoubtedly is responsible for the bulk of the WEE transmission to birds, horses, and man throughout its range in the western part of the United States. *Aedes* mosquitoes appear to play only a minor role in epidemic transmission.

Until a few years ago the distribution of WEE was believed to be limited to that of *C. tarsalis*. It is now known that it does occur in mosquitoes and birds in the East in the absence of *C. tarsalis*, however, but does not cause disease in man and is only rarely seen clinically in horses. In the East the enzootic status of WEE appears to be similar to that of EEE, with *C. melanura* in fresh-water swamps playing the role of the principal enzootic vector. The absence of a highly efficient epidemic vector, such as *C. tarsalis*, is probably the main factor in keeping the virus within discrete enzootic foci. Also, laboratory studies have shown that animals immune to EEE respond to WEE infections with significantly lower viremias. This may be a contributing determent to the epidemic spread of WEE in areas where a high proportion of birds and horses possess EEE antibody.

St. Louis encephalitis (SLE), like EEE and WEE, is primarily an infection of birds transmitted by mosquitoes, with man an unfortunate, accidental host. The virus of SLE differs from those of EEE and WEE, however, in having a reversed mosquito susceptibility range. It readily infects all species of *Culex* mosquitoes which have been tested, whereas EEE and WEE viruses find most *Culex* species (except *C. tarsalis*) almost totally refractory.

In the far west, *C. tarsalis* is the main vector of SLE and, as would be expected from the breeding habits of this mosquito, most of the human cases are rural. A different situation

exists in the central and east central States, where *C. tarsalis* is not abundant. There *Culex pipiens* or *Culex quinquefasciatus* are apparently the important epidemic vectors and a high proportion of the cases are urban or suburban.

The mechanics of an urban epidemic appear clear. Infected wild birds probably introduce the virus to high populations of suburban and urban *C. pipiens* or *C. quinquefasciatus*, which rapidly spread it to city-dwelling birds and chickens. These, in turn, serve as a ready source of infection for additional numbers of the mosquitoes. A consequence of the resultant bird epizootic is exposure of a large segment of the human population to infection by mosquito bite. The vectors responsible for the initial infection of the wild birds are unknown, but widespread sylvan mosquitoes may be involved.

Control measures through vector abatement are often economically impractical. Only urban SLE gives immediate promise of relatively inexpensive control. It is obvious, therefore, that continued investigations on the ecology of encephalitis are necessary.

Changing Picture of Murine Typhus

HARRY D. PRATT, *Communicable Disease Center, Public Health Service, Atlanta, Ga.*

The changing picture of murine typhus in the United States can be shown by comparing two 4-year periods, 1941–44 and 1953–56. In the first period the number of cases of murine typhus increased to a peak of 5,401 in 1944, while in the latter period the number of cases decreased to 98 in 1956. This is the first year since 1924 that less than 100 cases of murine typhus have been officially reported to the Public Health Service.

Treatment in the first period was largely symptomatic; today, broad spectrum antibiotics, such as chloromycetin, aureomycin, and terramycin, give quick and effective cures. The use of these new drugs, however, probably obscures the true incidence of the disease. They mask all types of rickettsia infection, making diagnosis with laboratory confirmation difficult or rare.

Prevention of murine typhus during the first 4-year period was based on controlling rat fleas, rat trapping, rat poisoning (using relatively ineffective rodenticides such as red squill), rat proofing, and sanitation. Today, in addition to these methods, there are powerful insecticides which control infected rat fleas for weeks or months. Many new rodenticides have been developed, particularly the anticoagulants, which control rodents effectively and thus limit the flea population.

Improved sanitation programs in cities throughout the United States, and increasing reliance of private industry on commercial pest control services, have probably had a long-term influence on the steady decrease of murine typhus.

John W. Cronin, 1905–1958

Dr. John W. Cronin, Assistant Surgeon General of the Public Health Service, and chief of its Bureau of Medical Services since November 1956, died of a heart attack March 26, 1958.

Born June 15, 1905, in Springfield, Ohio, he began his career with the Public Health Service in 1932. As chief of the Hill-Burton program from 1949 to 1956, he is credited with rallying State support for the construction and enlargement of hospitals, nursing homes, and clinics throughout the United States.

Dr. Cronin was a graduate of Miami University, Oxford, Ohio, and of the Cincinnati University College of Medicine.

publications

Home Accident Prevention Text

PHS Publication No. 564. 1957. 24 pages. 15 cents.

The Home Accident Prevention Text provides both guidance and reference suggestions for all categories of local public health workers whose cooperation will be required in a local home accident prevention program. Following an introductory survey of environmental, physical, mental, and emotional factors in home accidents, the booklet analyzes the roles of the health officer, public health nurse, sanitarian, and other health personnel. The important contribution of the private physician to the success of local programs and the value of cooperation with other agencies in the community are stressed.

One Way to Develop Local Home Accident Activities

PHS Publication No. 566. 1957. 10 pages. 35 cents.

Designed to aid local health departments, One Way to Develop Local Home Accident Activities outlines a "learning by doing method." It presents a four-point program: staff orientation, local resources, the local problem, and suggested activities.

Sources of Morbidity Data, Listing Number 5, 1957

PHS Publication No. 565. 1957. 81 pages.

This fifth listing of projects in the files of the Clearinghouse on Current Morbidity Statistics Projects describes 105 projects not previously reported. The projects are grouped according to the major type or types of disease, injury, or impairment with which they deal.

There are three indexes: the projects by type of data collection, the organizations and institutions responsible for the research, and the principal investigators. Also included is a section of supplementary notes on projects in progress when their descriptions were received by the clearinghouse for inclusion in previous listings.

Since the listings of the clearinghouse are published primarily for the use of actual and potential contributors, the number of bound copies for other distribution is limited. Tear sheets of the description of each study are available, however, to research workers or persons planning public health programs.

Survey of Compounds Which Have Been Tested for Carcinogenic Activity, Supplement 1

PHS Publication No. 149. Supplement 1. 1957. By Philippe Shubik and Jonathan L. Hartwell. 388 pages. $3.50.

This supplement surveys the literature from 1938 through 1943 on compounds that have been tested for cancer-producing properties in experimental animals. Having the same format as its predecessor, it combines in tabular form experimental data on nearly 1,000 compounds, of which about one-fifth are cancer-producing in animals.

The compounds are arranged alphabetically in classes, and the data cited include reference, species and number of animals, route of administration, number and type of tumors, and duration of experiment. A cumulative compound index, one of several indexes, includes the listings in both PHS Publication No. 149 and the supplement.

Because of the growing importance of chemicals in food, drugs, and cosmetics, and the increasing awareness of the possible long-range effects of these and other materials such as the products of combustion of tobacco and gasoline on the human organism, the book should be useful to anyone interested in environmental cancer as well as cancer investigators.

Research Grants and Awards, National Institutes of Health, 1957

PHS Publication No. 571. 1957. 147 pages. 45 cents.

Health research facilities grants, research fellowships, and research grants awarded by the National Institutes of Health during fiscal year 1957 are listed separately by State and institution.

Toward a Healthier World—Your Career in Sanitary Engineering

PHS Publication No. 579. 1958. 16 pages; illustrated. 25 cents.

This is the first career guidance pamphlet to describe sanitary engineering. Designed especially for high school students, it covers past achievements of sanitary engineers, their present and future work, the need for such engineers, salary, possible employers, and educational requirements.

This section carries announcements of new publications prepared by the Public Health Service and of selected publications prepared by other Federal agencies.

Unless otherwise indicated, publications for which prices are quoted are for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C. Orders should be accompanied by cash, check, or money order and should fully identify the publication. Public Health Service publications which do not carry price quotations, as well as single sample copies of those for which prices are shown, can be obtained without charge from the Public Inquiries Branch, Office of Information, Public Health Service, Washington 25, D. C.

The Public Health Service does not supply publications other than its own.

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